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HEALTH RELATED QUALITY OF LIFE AFTER CHILDHOOD CANCER

- A Finnish Nationwide Survey

by

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To survivors of childhood cancer

Susanna Mört

HEALTH RELATED QUALITY OF LIFE AFTER CHILDHOOD CANCER - A Finnish Nationwide Survey

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ABSTRACT

The purpose of this Finnish epidemiological nationwide cross-sectional study was to evaluate the Health Related Quality of Life (HRQL) of young people that have survived childhood cancer at least four years after cancer diagnosis. The study aims were (1) to increase knowledge and understanding about the relationship between childhood cancer and its treatment and HRQL of childhood cancer survivors and (2) to identify survivors who need and could benefit from ongoing long-term follow-up, as well as (3) to identify what kind of aftercare the childhood cancer survivors will possibly need.

HRQL and fatigue of currently still young survivors of extracranial childhood malignancies were evaluated with self-reports and parent proxy reports. HRQL was measured with age-appropriate generic instruments: PedsQL™, SF-36, 15D, 16D and 17D. Fatigue for children and adolescents aged below 18 years was measured with the PedsQL™ Multidimensional Fatigue Scale Finnish version. PedsQL™ parent-proxy and the PedsQL™ Multidimensional Fatigue Scale Parent-proxy instruments were used to assess the perception of the parents on HRQL and fatigue of their children and adolescents. Postal-survey questionnaires were mailed to 852 childhood cancer survivors aged 11-27 years and their randomly selected gender-, age and living-place matched controls, as well as under 18-year-old children´s parents. A total of 474 survivors, 595 controls, 209 survivor's parent and 253 control's parent replied. The mean age of survivors at the time of the study was 18.4 years. The mean length of survival was 12.3 years, and the mean age at diagnosis 5.5 years.

The most of the Finnish childhood cancer survivors evaluated that their HRQL as good. Survivors rated their HRQL equal or higher than their controls. The only dimension where the survivors scored poorer than the controls was the 15D mobility dimension. Survivors of childhood cancer did not suffer from significant fatigue. There were subgroups of childhood cancer survivors who had poorer level of HRQL, and suffered from fatigue more than the reference group. The demographic factors that associated with poorer HRQL were female gender, greater weight, living alone, need of remedial education, an additional non-cancer diagnosis, survivors with siblings, and self-reported unhappiness. Disease-related factors that associated with poorer HRQL were higher age at the time of diagnosis, the diagnosis of Wilms tumor, neuroblastoma, or osteosarcoma, and treatment with stem cell transplantation. The factors associated with more fatigue in survivors were male gender, older age at evaluation, the need of remedial education at school, lower overall average grade in the latest school marks report, length of survival more than 10 years, lower HRQL-scores, and a sarcoma diagnosis. However, all the used demographic and disease related factors explained only about one third of the variation in the HRQL scores. In open questions, the survivors were most worried about their physical health, but were also worried about their mental health, cancer inheritance, late-effects, and fertility and relapse issues. It seems that there are subgroups of survivors who need and could benefit from ongoing long-term follow-up. In the future, the survivors of childhood cancer need more information about their physical and mental health, as well as on their cancer inheritance, possible late-effects including fertility issues, and on the risk of relapse.

Keywords: childhood cancer, fatigue, Health Related Quality of Life, survivor

Susanna Mört

TERVEYTEEN LIITTYVÄ ELÄMÄNLAATU LAPSUUSIÄN SYÖVÄN JÄLKEEN - valtakunnallinen tutkimus Suomessa

Hoitotieteen laitos, lääketieteellinen tiedekunta, Turun yliopisto, Suomi

Annales Universitatis Turkuensis. Sarja-Ser D Medica-odontologica. Turku 2012.

TIIVISTELMÄ

Tämän epidemiologisen poikkileikkaustutkimuksen tarkoituksena oli evaluoida suomalaisten vähintään neljä vuotta lapsuusiän syöpädiagnoosista selviytyneiden nuorten terveyteen liittyvää elämänlaatua. Tutkimuksen tarkoituksena oli 1) lisätä tietoa ja ymmärrystä lapsuusiän syövän ja sen hoitojen ja terveyteen liittyvän elämänlaadun suhteesta toisiinsa, 2) identifioida ketkä lapsuusiän syövästä selviytyneet tarvitsisivat pitkäaikaisseurantaa ja mahdollisesti hyötyisivät siitä, sekä 3) identifioida minkälaista jälkihoitoa lapsuusiän syövästä selviytyneet mahdollisesti tarvitsevat.

Lapsuusiän syöpää sairastaneiden terveyteen liittyvää elämänlaatua mitattiin ikään sopivilla geneerisillä PedsQL™, SF-36, 15D, 16D and 17D itsearvionti mittareilla. Alle 18-vuotiaiden uupumusta mitattiin PedsQL™ Multidimensional Fatigue-mittarilla. Vanhempien arviointiin heidän lastensa terveyteen liittyvästä elämänlaadusta ja uupumuksesta käytettiin vanhempien arviointiin tarkoitettuja PedsQL™ ja PedsQL™ Multidimensional Fatigue Scale- mittareita. Suomalainen valtakunnallinen postikysely lähetettiin 852 syövästä selviytyneelle 11–27-vuotiaalle nuorelle ja heidän sukupuolen, iän ja asuinpaikan suhteen kaltaistetuille verrokeilleen, sekä alle 18-vuotiaiden lasten vanhemmille. Yhteensä kyselyyn vastasi 474 syövästä selviytynyttä, 595 kontrollihenkilöä, 209 syövästä selviytyneiden lasten vanhempaa ja 253 kontrollivanhempaa. Syövästä selviytyneiden vastaajien keski-ikä oli 18.4 vuotta, keskimääräinen diagnoosi-ikä oli 5.5 vuotta ja syövästä selviytymisestä kulunut keskimääräinen aika oli 12.3 vuotta.

Suurin osa suomalaisista lapsuusiän syöpää sairastaneista piti terveyteen liittyvää elämänlaatuaan hyvänä. Selviytyneet arvioivat terveyteen liittyvän elämänlaatunsa joko samantasoiseksi tai korkeammaksi kuin heidän kontrollinsa. Ainoana poikkeuksena oli 15D mittarin liikkumiseen liittyvä osaalue, jossa syövästä selviytyneet arvioivat terveyteen liittyvän elämänlaatunsa huonommaksi kuin heidän verrokkinsa. Syövästä selviytyneet eivät kärsineet myöskään merkittävästä uupumuksesta kontrolleihin verrattuna. Tutkimuksessa löydettiin kuitenkin syövän sairastaneita, joiden terveyteen liittyvä elämänlaatu oli huonompi ja jotka kärsivät enemmän uupumuksesta. Demograafisista taustamuuttujista naissukupuoli, korkeampi paino, yksin asuminen, tukiopetuksen tarve koulussa, jokin muu diagnoosi syöpädiagnoosin lisäksi, sisarukset sekä se, että ei tuntenut itseään onnelliseksi ja toisaalta syöpäsairauteen liittyvistä taustamuuttujista korkeampi diagnoosi-ikä, Wilmsin tuumori-, neuroblastooma- tai osteosarkoomadiagnoosi ja läpikäyty kantasolujensiirtohoito vaikuttivat huonontavasti syövästä selviytyneiden terveyteen liittyvään elämänlaatuun. Syövästä selviytyneiden lisääntyneeseen uupumukseen korreloivat miessukupuoli, korkeampi ikä, tukiopetuksen tarve koulussa, matalampi viimeisimmän koulutodistuksen keskiarvo, yli 10 vuoden aika syöpädiagnoosista ja sarkoomadiagnoosi. Tutkimuksessa käytetyt taustamuuttujat selittivät kuitenkin vain noin kolmanneksen syövästä selviytyneiden terveyteen liittyvän elämänlaadun vaihtelusta. Avointen kysymysten tulosten mukaan lapsuusiän syövästä selviytyneet olivat eniten huolissaan fyysisestä terveydentilastaan, mutta ilmaisivat huolensa myös psyykkisestä terveydentilastaan, syövän periytymisestä, myöhäisvaikutuksista, hedelmällisyydestä ja syövän uusiutumisriskistä. Syövästä selviytyneiden joukosta löytyy siis ryhmiä, jotka tarvitsisivat ja hyötyisivät pitkäaikaisseurannasta syövästä parantumisen jälkeen. Tulevaisuudessa syövästä selviytyneet tarvitsevat myös lisää tietoa fyysisestä ja psyykkisestä terveydentilastaan, sekä oman syöpäsairautensa periytyvyydestä, myöhäisvaikutuksista, vaikutuksista hedelmällisyyteen sekä syövän mahdolliseen uusiutumiseen liittyvistä asioista.

Avainsanat: lapsuusiän syöpä, terveyteen liittyvä elämänlaatu, selviytyjä, uupumus

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ABBREVIATIONS

ALL = Acute Lymphoblastic Leukemia

AML = Acute Myeloid Leukemia

B = unstandardized regression coefficient

CF = Cognitive fatigue in the PedsQL™ Multidimensional Fatigue Scale

FCR = the Finnish Cancer Registry

GF = General fatigue in the PedsQL™ Multidimensional Fatigue Scale

HL = Hodgkin Lymphoma

HRQL = Health Related Quality of Life

MCS = Mental Component Summary in SF-36

MMQL = Minneapolis-Manchester Quality of Life Instrument

NBL = Neuroblastoma

NHL = Non-Hodgkin lymphoma

NOPHO = Nordic Society of Pediatric Hematology and Oncology

PCS = Physical Component Summary in SF-36

Peds-Fact-Brs = Pediatric Functional Assessment of Cancer Therapy-Childhood Brain Tumor Survivor

PedsQL™ = Pediatric Quality of Life Inventory PedsQL Version 4.0™

PEDQOL® = The Quality of life in Children and Adolescents with Cancer

QL = Quality of Life

RBL = Retinoblastoma

SCT = Stem Cell Transplantation

SD = Standard deviation

SF = Sleep/rest fatigue in the PedsQL™ Multidimensional Fatigue Scale

SF-36 = Short Form-36 version 2™ Health Survey

TF = Total fatigue in the PedsQL™ Multidimensional Fatigue Scale

WHO = The World Health Organization

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, which are referred to in the text with Roman numerals:

I Mört S, Salanterä S, Matomäki J, Salmi T.T & Lähteenmäki P.M. 2011. Cancer related factors do not explain the quality of life scores for childhood cancer survivors analysed with two different generic HRQL instruments. Cancer Epidemiology, 35(2), 202-210.

II Mört S, Salanterä S, Matomäki J, Salmi T.T & Lähteenmäki P.M. 2011. Self-reported health-related quality of life of children and adolescent survivors of extracranial childhood malignancies: A Finnish nationwide survey. Quality of Life Research, 20 (5), 787-797.

III Mört S, Lähteenmäki P.M, Matomäki J, Salmi T.T & Salanterä S. 2011. Fatigue in young survivors of extracranial childhood cancer: A Finnish Nationwide survey. Oncology Nursing Forum, 38 (6), E445-454.

IV Mört S, Lähteenmäki P.M, Matomäki J, Salmi T.T & Salanterä S. Health related quality of life after childhood cancer: A Finnish Nationwide survey on parent-proxy reports. (Submitted)

1 INTRODUCTION

Improved survival rates together with awareness on physical and psychological late-effects have raised question about the health-related quality of life (HRQL) of survivors of childhood cancer (Eiser 2009). Although the word "cancer" conveys a life-threatening illness (Bryant 2003), the long-term cure is a realistic and possible aim for many (Eiser 2004). The treatment of childhood cancer has improved during the last three decades, mainly due to modernized treatment, the centralization of care, the improvement of supportive care, unified treatment protocols and clinical trials (Maurice-Stam 2007). For children and their families the information about survival rates may be of varying comfort. According to recent estimates, with new technological advances the five-year childhood cancer survival rate has at times risen over 80% in children, adolescents and young adults in Finland (Gatta et al. 2009).

Childhood cancer is usually defined as a malignant disease that is diagnosed up to 16 years of age. The causes of childhood cancer are unknown. The incidence of childhood cancer has been stable for many decades and each year approximately 150 children are diagnosed with cancer in Finland. Due to the fact that survival rates have continued to increase, there is a growing group of childhood cancer survivors who could live several decades after diagnosis.

Unfortunately, surviving childhood cancer is not always the same as a total cure (Van Dongen-Melman 2000). Cancer itself and different treatment modalities are aggressive. They may cause several physical-, psychological, and social late-effects in children. The type and length of treatment depend on a number of factors such as the type of cancer, location and stage of disease (Maurice-Stam 2007). Chemotherapy, surgery and radiotherapy are typically the major treatment modalities implemented. When cancer is diagnosed in childhood or adolescence, a time when young people are usually confronted with developmental tasks, they may get more disrupted and experience increased psychological distress even long after being cured. (Michel et al. 2010) Therefore, it is worthwhile to notice that childhood cancer experience does not stop just by virtue of survival (Casillas et al. 2006, Shepherd & Woodgate 2010) and all survivors suffer from some kind of stigmatizing effects of childhood cancer that will have an impact on their later life (Lähteenmäki et al.1999, Parsons & Brown 1998). The lifestyle choices, like education or decisions about their future life, may be significantly affected by their cancer experiences (Prouty et al. 2006). The improving survival rates provide no information about the expected HRQL (Zebrack & Zelter 2003). Hence, in recent years the question how long the patients are surviving has shifted to question how well the patients are surviving (Jacobsen & Jim 2011). The long- term effects of childhood cancer and its treatment are significant and need further investigating.

The best possible way to evaluate the long-term effects is to ask the childhood cancer survivors themselves. One way to analyse survivors' late-effects is to assess their health-

related quality of life (HRQL). HRQL is nowadays an important outcome indicator in evaluating health-care interventions and treatments and in understanding the burden of disease (Hinds et al. 2004, Solans et al. 2008, Varni et al. 2001). However, in previous studies the perspective has often depended on parent-proxy-reporting (Meeske et al. 2004, Schultz et al. 2007, Speechley et al. 2006). Thus, there is a need for getting more information about young survivors' HRQL estimated by the young survivors themselves.

In previous HRQL studies of childhood cancer survivors, there is a mixture of different methodologies with inconsistent findings. Nevertheless, the findings regarding the determinants of childhood cancer survivors' HRQL are ambiguous (Klassen et al. 2011).

We strive for a better understanding of the relationship between childhood cancer and HRQL of childhood cancer survivors. Comparison with the perceptions of general population could help to identify survivors who need and could benefit from ongoing long-term follow-up. This understanding could help nurses, public health nurses, as well as other health care professionals to develop more efficient psychosocial aftercare for childhood cancer survivors in the future, so that good evidence based physical and psychosocial care can be provided to support and enhance survivor's HRQL.

2 BACKGROUND OF THE STUDY

2.1 Childhood cancer and survival

2.1.1 Childhood cancer and its treatment

Childhood cancer is usually defined as a malignant disease within the age group from 0 to 16 years of age (Weiner 2002). In spite of childhood cancer is generally talked about like in a single disease, there are different cancer types. Table 1 shows general information about the different childhood cancer types and incidence in Finland in the year 2009. Leukemias, central nervous system (CNS) tumors, and lymphomas are the three most common malignancies in children. Those cover about two-thirds (66%) of all cancers diagnosed in 0-14 year old. (Childhood cancer statistics – incidence, Cancer Research UK 2011) The incidence of cancer diagnoses varies across the age groups. Younger children have more acute lymphoblastic leukemia (ALL), CNS tumors, neuroblastomas and Wilm's tumors whereas older children have more commonly diagnoses such as Hodgkin's lymphoma and bone tumors (Maurice-Stam 2007). Types of childhood cancer differ also in terms of survival rates, the consequences of treatment, and associated complications (Eiser et al. 2002).

Childhood cancer is a rare event. The population of Finland is 5.3 million, of which 1.1 million are children. Each year, approximately 150 new childhood cancer cases are diagnosed in Finland (Finnish Cancer Registry 2007), and roughly 100 cases of them are extracranial. Almost half of the extracranial childhood cancer diagnoses are leukemias. The incidence of childhood cancer in Finland and other Nordic countries has been quite stable since the 1950s. (van der Horst et al. 2006), but in many countries there is an increase in childhood cancer incidence. For example, in Great Britain between 1966 and 2000 there has been an average increase of less than 1% per year. The majority of childhood cancers are malignant. (Childhood cancer statistics – incidence, Cancer Research UK 2011) The causes of childhood cancer are unknown. There are hypotheses such as environmental factors or early exposure to infection and the subsequent effects on the immune system. Despite many attempts, the results of studies have been inconsistent and the firm conclusions of the causes and risk factors remain undetermined. However, some inherited diseases are associated with an increased risk of malignancies. In retinoblastoma, for example, a family history is found in about one-third of the cases. (Eiser 2004) A person with Li Fraumeni syndrome or Down syndrome has an increased risk of developing cancer (Betz & Sowden 2008, Bhatia 2004). Even though the risk of getting cancer in the siblings of childhood cancer patients is twice as high as in general population, it is still almost negligible due to low incidence of childhood cancer (Eiser 2004).

Childhood cancer differs inherently from the cancers of adults. Childhood cancer can more often be cured. Children are able to tolerate more aggressive therapy than adults, but at the same time, aggressive treatments leave them at risk for long-term residual complications. Another special characteristic is that as children are at a growing age, the side-effects of treatment may be more significant than in the adults. (Eiser 2004).

Table 1. General information about the different childhood cancer types and incidence in Finland in the year 2009

Childhood cancer types	**Incidence in 2009* (n=146)**	**Treatment and average treatment time****	**Typical age at diagnosis*****
Leukemias	**53**	Chemotherapy, sometimes with radiotherapy	
-ALL	45	30 months	2-4 year
-AML	7	8 months	< 3 year
-Other leukemias	1		
Lymphomas	**15**	Chemotherapy, sometimes with radiotherapy	
-Non-Hodgkin lymphoma	8	4-30 months	< 3 year
-Hodgkin lymphoma	7	2-6 months	>10 year
Neuroblastoma	**7**	Surgery, chemotherapy and sometimes radiotherapy < 12 months	< 3 year
Wilms tumor	**8**	Surgery, chemotherapy and sometimes radiotherapy < 12 months	< 5 year
Retinoblastoma	**4**	Surgery or radiotherapy, sometimes chemotherapy Treatment time depends on the protocol needed.	< 3 year
Sarcomas	**12**	Chemotherapy and surgery, sometimes with radiotherapy (radiotherapy not in Osteosarcoma)	
Bone tumors	4	< 12 months	
- Osteosarcoma	2		≥10 year
- Ewingin sarcoma	2		≥ 7 year
Soft tissue sarcoma	8		
- Rhabdomyosarcoma	5		<10 year
- Other soft tissue sarcomas	3		>8 year
Others	**14**	Surgery or chemotherapy, sometimes radiotherapy < 12 months	Differs between age and gender
-Germ cell tumors	2		
-Others	8		
-Hepatoblastoma	4		
CNS	**33**	Surgery, sometimes chemotherapy and/or radiation Treatment time depends on the protocol needed.	Differs between the type of cancer

*Finnish cancer Registry statistics (personal communication, Professor Risto Sankila)
** Pizzo & Poplak 2010
***Childhood cancer statistics – incidence, Cancer Research UK 2011
ALL= Acute Lymphoblastic Leukemia, AML= Acute Myeloid Leukemia, CNS= Central Nervous System

Children with cancer are typically treated according to treatment protocols that have been developed through international research and co-operation. Due to the rareness of childhood cancer, the centralization of childhood cancer care is considered important and it has resulted in more rapid accumulation of expertise and progress in treatment. (Eiser 2004) In Finland, the care of children with cancer is the responsibility of five University hospitals (Helsinki, Kuopio, Oulu, Tampere, and Turku). Chemotherapy, surgery and radiotherapy are the major treatment modalities used. The standard practice involves a combination of those modalities. For example according to the NOPHO (Nordic Society of Pediatric Hematology and Oncology)'s – ALL 2008 treatment protocol, ALL is usually treated with chemotherapy alone whereas solid tumors are treated with surgery combined with chemotherapy and/or radiotherapy (Pizzo & Poplak 2010). Again, hematological malignancies need treatment intensification with allogenic stem cell transplantation (SCT) if the initial risk classification shows the very high risk of a relapse (a reappearance of cancer) or if the disease has already relapsed. For solid tumors, very intensive chemotherapy with autologous stem cell rescue may be used if the malignancy is widely spread at the time of diagnosis and in recurring cases. (Pizzo & Poplak 2010) Hence, the type and length of treatment depends on a number of factors such as the type of cancer, location and stage of disease (Maurice-Stam 2007).

Side-effects of cancer treatment are common although the development of more effective and targeted therapies has reduced them to some extent. Side-effects can occur within days or weeks of initial treatment (early side-effects), or even months to years after the end of treatment (late side-effects). (Maurice-Stam 2007) The most common early side-effects include immunosuppression and infections, nausea and vomiting, anemia, thrombocytopenia, malnutrition, pain and all different psychosocial aspects of the illness (Bryant 2003). Cancer relapse is also possible (Eiser 2004, Pizzo & Poplak 2010). Approximately 8-12% of children will experience a relapse in 20 years, which is 10-15 times greater than the cancer risk of age-matched controls (Bradley 2002).

2.1.2 Children and adolescents with cancer

Cancer and its treatment is a major challenge to a child (Eiser et al. 2002). A child with cancer has to make repeated hospital visits and experience painful treatment (Eiser et al. 2002, Eiser 2004). A child has to experience numerous and complex psychological, physical, school-related, and behavioural symptoms and problems during and after treatment for cancer. (Eiser 2004, Ruland et al. 2009). For example, in the literature review by Ruland et al. (2009), children with cancer (7-12 years old) could identify 219 distinct symptoms or problems associated with cancer and its treatment. Symptoms may be related directly to cancer, such as tumor pain, or may occur as a consequence of the treatment such as nausea (Linder 2005). Treatment will inevitably cause limitations to a child's social life and activity level, and they have to face considerable uncertainty about the future (Eiser 2004, Eiser et al. 2002). The illness will affect various aspects of daily living and therefore potentially degrade their quality of life (QL) (Taylor et al. 2008).

A child's reaction to cancer depends on their developmental level, temperament, available coping mechanisms, and the condition itself. A child's conceptual understanding of their own illness is based not only on their age and developmental level, but also on duration and type of experiences accumulated while living with the disease. (Wong et al. 2006) When cancer is diagnosed in childhood and adolescence, a time when young people are usually confronted with developmental tasks, they may get more disrupted and experience increased psychological distress even long after being cured (Michel et al. 2010). They have increased risk also for behaviour and emotional problems (Wong et al. 2006). The serious illness will change a young person's outlook of life (Taylor et al. 2008). It is hypothesized that a child may adopt a coping strategy for shielding her/him from the effect on the illness (Harding 2001). If there are negative aspects impacting on the young person's life, they try to adapt their behaviour as more acceptable. Also friends and family are important mediators of how a child with cancer will view the life. (Taylor et al. 2008) An attitude to illness of the child depends on the parent's attitude and behavior towards it. Being with friends and gaining their acceptance is important to young person. If the friends treat the patient as before, it is easier for the patient to accept her/his illness. (Taylor et al. 2008a)

The crisis of childhood illness and hospitalization affects each family member when one member of the family is diagnosed with cancer (Ganz 2001, Lindahl et al. 2008). Parents of cancer patients must cope with the emotional strain of assisting their child through diagnosis, treatment and sometimes relapse or death (Eiser et al. 2002). They usually try to learn about their child's diagnosis, they have to adapt to emergency situations and experience trying events (Pöder et al. 2008). Denial, anger, fear, anxiety, and frustration are common feelings expressed by parents (Bryant 2003). Additionally, parents can feel guilty because they feel helpless to alleviate the child's physical and emotional pain (Wong et al. 2006). Families face a major challenge acknowledging the limitations caused by the disease, and on the other hand, try to maintain as normal a life as possible (Eiser 2004). Parents spend lengthy periods in the hospital with the child and they have to face a possible financial burden associated with lost work opportunities and the increased cost associated with travelling, and cancer care (Eiser 2004, Lähteenmäki et al. 2004a). Lähteenmäki et al. (2004a) found out that in spite of the monthly Finnish social security reimbursement to each family with childhood cancer, the perceived amount of lost income was especially high during soon after cancer diagnosis. The main reason for this was that several mothers either stopped working or diminish working time. The same study also highlighted that cancer parents rated their own health significantly more negative than control group parents. For parents, the major challenge is that they have to face an extended period of uncertainty regarding the child's health, and life-threatening nature of cancer. (Eiser 2004) Uncertainly is often present and it can affect several aspects of children's lives and the lives of their family (Shepherd & Woodgate 2010).

Siblings are also affected by having a different brother or sister, and they may simultaneously feel guilt and anger or even jealousy toward their ill sibling. Additionally,

they may suffer from secondary losses such as the ability to participate in extracurricular activities or social events because of the ill sibling. (Wong et al. 2006) Lähteenmäki et al. (2004b) found that the siblings below school age, when assessed three months after their cancer diagnosis, tended to have conduct problems and other behavioral problems. These symptoms, however, became less evident during a one-year follow-up. The school aged siblings suffered conduct, learning, and psychosomatic problems as well as impulsive-hyperactive and other behavior symptoms, which remained throughout one year follow up time.

2.1.3 Surviving of childhood cancer

The term survivorship is undefined and it has been described in a variety of ways. Mullan (1985) divided survivorship into separate phases. The first phase is acute survivorship, which begins with a diagnosis of cancer and continues with treatment. Fear and anxiety are constant during this phase. The second phase is when the patient completes the course of treatment or goes into remission. This time the recovery, rehabilitation and a "new normal" way of life are important. Permanent survival is the final phase of survival and it is often called cure. Miller et al. (2008) suggested that there also are three different extended survivorships and four different permanent survivorships. Extended survival includes the survivors of maintained remission, the survivors free of cancer, or the "survivors" who are living with cancer for long periods of time. Permanent survival defines a heterogeneous group of survivors. There are some who are healthy and have moved beyond cancer, some suffer long-term late-effects, and some who re-enter the system later with a second cancer that is related or unrelated to their previous cancer and its treatment. However, this suggestion is made for adult population and maybe not directly applicable to young childhood cancer survivors. Doyle (2008) determined that cancer survivorship is a process of life-changing experiences that begins at diagnosis. It also involves uncertainty and has both positive and negative aspects.

The cure and long-term survival rates of childhood cancer are often based on five-year survival from diagnosis (Novakovik 1994). In historical perspective, children who got a cancer diagnosis five decades ago did not have much hope for a cure. Survival rates have improved steadily since the 1960s (Eiser 2004), when the introduction of chemotherapy and radiotherapy resulted in remarkable increases in survival rates. (Maurice-Stam 2007) In the early 1970s, five year survival rates were less than 10% (Steinhorn 1984) and according to recent estimates, the five-year survival rate depending on the cancer has become as great as 81% in children (0–14 years) and 87% in adolescents and young adults (15–24 years) (Gatta et al. 2009).

Survival rates vary according to specific type of childhood cancer and also countrywide. Some cancer types like late age diagnosed neuroblastoma remain very difficult to cure, and in some cancer types the survival rates are as high as 90% or over. Coebergh et al. (2001) compared variation in the survival rates of European children diagnosed ALL in 1978-1992. In that time five year survival rates with ALL in Finland was 81% while for

example, in Estonia was only 34%. Gatta et al. (2003) compared survival rates between young patients diagnosed childhood cancer in 20 European countries during the period 1990–1994. They found that the five-year survival variation in childhood cancer was large between countries: from 45% in Estonia to 90% in Iceland. In Europe, the five-year survival rate was 71.8%. The Nordic countries had the highest survival figures. It was concluded that the Nordic countries represent a survival gold standard amongst other European countries. However, the survival gap between countries has recently reduced between the European countries (Gatta et al. 2009).

Cancer is no longer necessarily considered a life-threatening disease, but moreover a chronic condition. Changes in treatment and improvements in survival mean that cancer now shares characteristics with other chronic conditions that affect children such as asthma or diabetes. Chronic conditions are characterized by the period of relatively good health and others of poorer health. However, cancer differs from other chronic conditions as treatment for cancer is shorter, but more aggressive, than for other conditions. The long-term cure is a realistic and feasible aim for many. For families, information about survival rates may provide varying levels of comfort. However, even if 80% of children survive, 20% do not, and at the time of diagnosis no one can say what will happen to any individual child with any certainty. (Eiser 2004) Thus, the word "cancer" still represents a life-threatening illness (Bryant 2003).

2.2 Health related quality of life and its assessment

2.2.1 The concepts of quality of life and health related quality of life

The concept of ***Quality of life*** (QL) was identified in Greek philosophy, but the phrase became popular after the Second World War (Campbell 1976). Nowadays, QL is a commonly used phrase (Taylor et al. 2008) and cited in everyday life in newspapers, on television, as well as in professional publications (Haas 1999). Although QL is a commonly used phrase, it is without a universal definition. QL is recognised as an abstract concept that is personal and unique to each individual. (Taylor et al. 2008) In the widest thought, there could be as many quality of life definitions as people, emphasising the basic default that individuals differ in what they find important (Liu 1976).

The ontological question in the QL discussion could be for instance: "What is the nature of the goodness of well-being?" It is an interesting fact that even in spite of many historical attempts there is no consensus about the nature of good life. (Nordenfelt 1999) In the literature, it can be found three different competing views about the idea of the good life; perfectionism, hedonism and welfarism. The perfectionisms' view has the idea that a person lives a good life when she/he realises important human potentials. The hedonism's view has the idea that a person lives a good life when she/he has a certain pleasant state and is able to avoid painful and unpleasant ones. Welfarism has the idea that a person lives a good life when she/he manages to get what they want. (Sandoe

1999) The lack of consensus about the goodness of well-being also holds for the modern scientific notion about QL (Nordenfelt 1999). It is thought that the QL depends on the cultural, spiritual, (Mandzuk & McMillan 2005) social and historical circumstances in which we find ourselves (Maurice-Stam 2007). QL is also understood to be on a continuum, dynamic (Haas 1999, Mandzuk & McMillan 2005) and value-laden (Haas 1999). It may range on a continuum from high to low, but it is never absent. Thus, major antecedent to QL is life itself. (Haas 1999)

In everyday language, QL could mean same as happiness, material wealth, and relationships with family and friends (Eiser & Morse 2001a). The QL is often used interchangeably with terms that have conceptually similar meanings, such as life satisfaction, well-being or functional status. However, while each of these terms could be one component of QL, they do not fully explain or define QL. Happiness is related and connected to QL, and may be a part of QL. (Haas 1999) For instance, if a person evaluates their QL as high, they are probably happy and satisfied (Mandzuk & McMillan 2005). Happiness is not necessarily an evaluation of a person's whole life, but rather on her/his feelings about one aspect of her/his life. That is, those terms lack the multidimensional character of QL, and although terms may affect life, it is not the same as QL. (Haas 1999)

From scientific literature focusing on adults, one can identify several concept analyses about QL. The World Health Organization (WHO) defines QL as "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns" (WHOQL Group 2004). Felce and Perry (1995) defined QL as "an overall general well-being that comprises objective descriptions and subjective evaluations of physical, material, social, and emotional wellbeing together with the extent of personal development and purposeful activity, all weighted by a personal set of values". Haas (1999) conducted a conceptual analysis of QL within the literature of health care from nursing, medicine, psychology, and social science and concluded that "QL is a multidimensional evaluation of an individual's current life circumstances in the context of the culture in which they live and values they hold. QL is primarily a subjective sense of well-being encompassing physical, psychological, social, and spiritual dimensions. In some circumstances, objective indicators may supplement or, in the case of individuals unable to subjectively perceive, serve as a proxy assessment of QL."

The concept of ***Health related Quality of Life*** (HRQL) draws on ideas from philosophy, economics, sociology and psychology, as well as medicine (Eiser & Morse 2001a) and nursing (Plummer & Molzahn 2009). QL research began in the disciplines of sociology (Mandzuk & McMillan 2005) and psychology, and it soon became an issue also within the health care (Haas 1999). The interest of QL research arose when technological advancements led to increased life span, and it was observed that increased length of life was not always desirable. (Haas 1999) With new technological advances, a problematic question was raised in health care; a person could be cured, but at what price?

In research and literature on health care, the terms QL and HRQL are often used interchangeably (Taylor et al. 2008). However, the term QL has been criticised as too general to be used in health care, and the global QL should be differentiated from HRQL (Haas 1999). It has been proposed that QL has sociological, economic, psychological, philosophical and ethical perspectives. Also health has emerged as an important but distinct perspective. (Taylor et al. 2008) In 1994, the First International Conference in Brussels on HRQL was an attempt to explicate and to include health related issues to the construct of QL. It was realized that all aspects of a person's life may legitimately affect their QL. For that reason, the term HRQL was adopted instead of the narrower phrase QL. (Sredl 2004) When the QL includes all aspects of life including the environment or externalities outside the context of healthcare, the HRQL focuses on health concept and on the field of health outcomes (Patrick 2003). It refers to the impact of health and illness on a person's QL (Eiser and Morse 2001a). Aaronson et al. (1991) concluded that "HRQL is a multidimensional concept that includes the broad areas of functional status, psychological and social well-being, health perceptions, and disease- and treatment-related symptoms". It is also stated that the HRQL is a multidimensional concept, which comprises the patient's perceived health status and well-being (Langeveld et al. 2004). Regardless of many attempts in last decades, there still is no universal accepted definition of QL or HRQL.

The interest in children's QL research did not arise until in the 1980s. Efforts to describe children's QL were invariably focused on functional problems, and the clinicians made the assessment for child's QL. (Eiser & Morse 2001a, Eiser & Morse 2001b) As was the case with adults, the interest of children's QL arose from possibilities brought about by new treatments and medicines which particularly increased the survival rates of previously fatal or chronic illness. For example, in pediatric oncology, the survival rates have increased significantly in four decades (Gatta et al. 2003, Gatta et al. 2009). This being stated, the domains of child's QL were mostly raised in areas of health care literature such as oncology and chronic illness (Mandzuk & McMillan 2005). Professionals also increasingly recognize in other health care areas that to treat a child's physical illness is not enough because the child's total well-being is affected by their illness and vice versa (Harding 2001).

Previous definitions of QL and HRQL are derived from concept analyses with adult populations, and they do not adequately represent the experiences of children, adolescents (Koot & Wallander 2001) and young people with chronic illness (Taylor et al. 2008). The attempts to define the HRQL of children and adolescents are still rare in literature. The concept analyses that are based on adult literature do not take into consideration developmental changes, language level, or young people's construction of health and illness. (Taylor et al. 2008) However, there are some analyses of HRQL from the child's point of view. Eiser (1996) defined that "HRQL is regarded as the impact of illness or treatment on specific aspects of the child's functioning". Bradlyn et al. (1996) noted that "QL in pediatric oncology is multidimensional. It includes, but it is not limited

to, the social, physical and emotional functioning of a child and adolescent, and when indicated, his/her family." Taylor et al. (2008) defined in their concept analysis of HRQL in young people with chronic illness that "HRQL in young people with chronic illness is subjective, multidimensional and dynamic. It is unique to each individual young person and includes aspects of physical, psychological and social function. It is dependent upon not only the stage of development but also the illness trajectory. This involves the achievement of goals and aspirations and constraints imposed through ill-health and treatment". This latest analysis from the existing definitions can perhaps be best adapted also to the children and adolescents' surviving cancer, and it is adapted as the basis for our study. Figure 1 shows the aspects and factors which form subjective HRQL in young people with chronic illness. The young person's unique life includes three aspects; the physical, psychological and social function. The stage of development and the illness trajectory factors involve the HRQL, and the significance of those factors may vary at different time points in life. The subjective HRQL forms an equation of these aspects and factors.

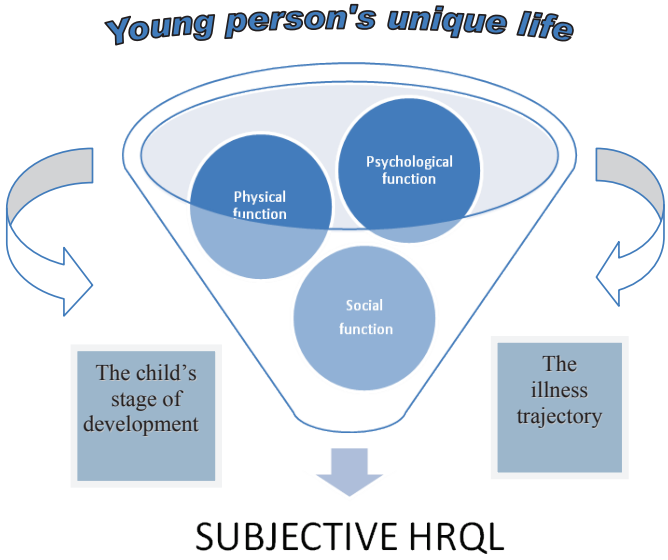


Figure 1. The aspects and factors which form subjective HRQL in young people with chronic illness (adapted from Taylor et al. (2008) concept analysis of HRQL in young people with chronic illness.)

2.2.2 The assessment of health related quality of life

Assessment of HRQL is increasingly acknowledged as an important health outcome measure in clinical trials, (Hinds et al. 2004, Varni et al. 2001) epidemiological studies and health surveys (Solans et al. 2008). HRQL measurement may be useful in routine audit work to understand the patient's perspective (Eiser & Morse 2001a), to facilitate communications between the patients and health care staff and to identify hidden or

unexpected health problems as well as to help in monitoring changes in patients' health state or in detecting responses to treatment (Higginson et al. 2001). Additionally, HRQL assessment is important because the healthcare personnel must determine how far treatment and disease compromise the HRQL and this determination may assist decisions about the rationing of resources (Eiser & Morse 2001a).

When the major antecedent for QL is life itself, the other is the involvement of someone with the cognitive ability to perform the evaluation (Haas 1999). Like Felce and Perry (1995) noticed, in a model of QL it is proposed that it integrates objective and subjective indicators. In the literature, there seems to be a consensus that purely objective measure is not enough (Nordenfelt 1999), and ideally, each individual evaluates their own HRQL. There are, however, situations were persons may not be able to describe their HRQL, such as persons with cognitive impairment, children with very young age, persons too ill or unable to answer themselves. Then other individuals such as caregivers or health care professionals may make the judgements of the person's HRQL. (Fitzpatric 1999, Eiser & Morse 2001b)

HRQL is not easy to measure, and there are some problems when assessing HRQL. The first problem is whether the person is asked to assess their situation in as neutral terms as possible (e.g. "I cannot move around as much as I could before"), or whether they are supposed to evaluate it in normative terms (My present disability to move makes my life miserable). It is often asked to make "an objective assessment about their symptoms or disabilities" and rarely asked whether the symptom or disability is particularly disturbing to their way of live. (Nordenfelt 1999) Added to this, the QL/HRQL can also be measured in objective terms such as absence or presence of illness/disability, or in subjective or perceived terms such as satisfaction with various aspects of life (Livingstone et al. 2007). The second problem is whether the subject assesses the overall state of their health, or their overall situation of well-being, or just certain relevant parts? Here the problem is, can the parts be isolated or is it reasonable to try to isolate various parts of life? (Nordenfelt 1999) The third problem is that the measuring of HRQL is vulnerable to a very basic epistemologically-based question: "How can we know with confidence that the results of this questionnaire accurately represent the QL/HRQL of an individual?" (Fitzpatrick 1999) Lastly, it is not enough to assess to what extent, for example, a person's mobility is affected by the disability or illness, but it is also important to estimate how that qualitatively affects the person's life (Harding 2001).

Even more challenging than the aforementioned problems with measuring adults' HRQL is the question of how to measure children and adolescents' HRQL. The measurement of HRQL in children has received less attention from a historical perspective than it has in adults. The assessments of QL in children and young people were developed in Europe and the USA during the 1980s and 1990s (Harding 2001). Early measures of HRQL in children were largely disease specific (Harding 2001) and the clinicians made the assessment for child's HRQL (Eiser & Morse 2001a).

There are special issues to be considered when assessing QL in children. Firstly, childhood through adolescence represents a time of significant variation in cognitive abilities both within and across developmental stages. (Linder 2005) That is why the measures of QL should reflect the child's level of understanding (Harding 2001). It is obvious that different age-groups need different instruments (Maurice-Stam 2007), and the instruments have to be written at the appropriate developmental level (Linder 2005). Because children think in more concrete terms, the subjective symptoms like fatigue need to be addressed in a manner meaningful to the child. Instruments should be completed easily and within a relatively short period of time. (Linder 2005) Secondly, it is not easy to know the questions which are specific to children. In particular, dimensions which are important for QL early in life may be less important later on, and vice versa. (Harding 2001, McDougall & Tsonis 2009). Hence, children should be involved in the critical stages in the instrument development process and in the phases of item reduction and validation (Solans et al. 2008).

It is also important to consider the proxy ratings as substitutes for ratings made by children themselves if the child is too young or too ill to complete the questionnaire themselves (Eiser & Morse 2001a, Maurice-Stam 2007) As Bradlyn et al. (1996) noted, "measurement of QL must be from the perspective of the child, adolescent and family and it must be sensitive to the changes that occur through development." However, parents perceive an illness usually to have more negative consequences than children themselves, and the clinicians usually either underestimate or over-estimate their patients' HRQL (Eiser & Morse 2001a). Upton et al. (2008) aimed to systematically review the literature published since 1999 on pediatric HRQL in relation to parent-child agreement. They noticed that parents of children in a non-clinical sample tended to report higher child HRQL scores than children themselves, while parents of children with health conditions tended to underestimate child HRQL. Eiser & Morse (2001b) also determined in their systematic review the relationship between ratings of children's HRQL made by parents and children. They reported that there was a greater agreement for observable functioning (e.g. physical HRQL) and less for non-observable functioning (e.g. emotional or social HRQL). Agreement was better between parents and chronically ill children compared with parents and their healthy children. Hence, it is strongly recommended that the HRQL should be measured with both the self-assessment as parent assessment (Felce & Perry 1995, Eiser & Morse 2001b, Upton et al. 2008).

2.2.3 Instruments for measuring health related quality of life

In literature, there is heterogeneity in the content and in the number of dimensions of QL/HRQL instruments. This heterogeneity is a consequence of confusion regarding the definition of QL/HRQL, differences in instrument development process, the theoretical framework applied, the target population, and/or the instrument's focus (Solans et al. 2008). There is a great diversity of QL measures, which likely reflects the theoretical basis of each measure, as well as the importance of the qualitative dimension assessed

by the developer of the instrument (Harding 2001). Additionally, the concept of QL has often been measured with terms of health-related concepts (McDougall & Tsonis 2009). Davis et al. (2006) did an outstanding finding in their review article, where they identified 14 generic and 25 condition-specific QL instruments for children aged 0-12 and even found eleven types of definition and three theories of QL. Usually, most of the QL instruments used in health care are not clear in their conceptual framework (Nordenfelt 1999). However, Fitzpatrick (1999) stated an interesting idea that, because there cannot be any absolute criteria or gold-standard for good life, it is not necessary to define and operationalize QL perfectly. In addition, it is also possible that an instrument can have good psychometric properties but yet poor conceptual framework (Davis et al. 2006). Hence, it is obvious that the comparisons of HRQL research results are difficult. It is suggested that researchers could report on which particular aspect of QL/HRQL they were assessing and the means by which it was measured (Haas 1999). When selecting HRQL instruments one must consider whether the instrument suits the purpose of the study and whether the dimensions covered are relevant to the context (Solans et al. 2008). To be a useful instrument, it is necessary that the measure detects clinically significant changes in the study population (Pearce et al. 2008).

Solans et al. (2008) did a systematic review of generic and disease-specific HRQL instruments in children and adolescents. They based their review on three previous reviews (Eiser et al. 2001c, Harding et al. 2001, Rajmil et al. 2001) and their new literature search. They tried to identify all HRQL instruments for children and adolescents developed or published between 1980 and 2006. They identified 94 instruments, from which 30 were generic and 64 disease-specific instruments. They concluded that HRQL instruments are generally multidimensional and designed to measure the respondent's subjective point of view regarding the impact of disease and treatment on physical, psychological, and social functioning. The production of HRQL instruments for children has continued to grow in recent years, especially the disease-specific versions (Maurice-Stam 2007, Solans et al. 2008). However, all the previous efforts in the assessment of QL/HRQL are not yet sufficiently integrated into the paediatric field (Eiser & Morse 2001). Even nowadays, there is still a limited availability of instruments for self completion by children (Solans et al. 2008).

There are two different types of HRQL instruments, *generic and specific instruments.* The generic instruments could be either health profiles or utility measures. The most common specific instruments are disease-specific or domain/dimension-specific. Both generic and specific instruments can be used to compare HRQL between patients at the point in time (discriminative instruments) or to measure longitudinal changes in HRQL within patients during a period of time (evaluative instruments). (Guyatt et al. 1993)

Generic instruments are useful in situations where it is important to be able to measure QL across different conditions and across different cultures (Harding 2001). Those instruments are particularly useful for surveys that attempt to document the range of disability in general population or in a patient group (Guyatt et al. 1993). Generic

instruments may assess QL across wide range of health problems (Fitzpatrick 1999) but they may not be sensitive to small changes in person's functioning (Harding 2001) or may be unresponsive to changes in specific conditions (Guyatt et al. 1993, Harding 2001). Health profiles are instruments that attempt to measure all important aspects of HRQL. In health profiles, the items are equally weighted, which assumes that their value is equal. The other type of generic instrument is utility measurement, which the HRQL is summarized as a single number along a continuum that usually extends from death (0) to full health (1). Utility scores reflect both the health status and the value of the health status to the patient. (Guyatt et al. 1993) Generic utility measures attempt to elicit overall global preferences felt by respondents for their health states (Fitzpatrick 1999). Utility scores could also be a previously estimated scoring function derived from results of preference measurements in groups of other patients or the community. The value of the importance of each item is calculated in relation to the others, but instruments with a single number do not show the domains in which improvement or deterioration occurs. (Guyatt et al. 1993)

Specific instruments may be specific to one disease (such as cancer), to a population of patients (such as childhood cancer patients), to a certain function (such as sleep), or to a specific problem (such as pain) (Guyatt et al. 1993) or the instrument could be specific for certain age. Disease-specific instruments provide more specific information that is clinically relevant, but not allow for comparisons between illness groups or to a healthy population. (Spieth & Harris 1996) Domain- and dimension-specific instruments measure a single dimension of HRQL such as pain or mood (Fitzpatrick 1999). Specific instruments can also be utility or individualized instruments. The last one assesses QL in terms of unique priorities of each respondent (Fitzpatrick 1999).

When choosing the instrument, it is essential that the instrument is reliable and valid for measuring HRQL in a given study population. Reliability refers to how consistently the measurement technique measures the concept of interest. Reliability testing focuses on three aspects of reliability: stability, also called test-retest reliability, equivalence and homogeneity. Test-retest reliability comprises of with the consistency for repeated measures of the same attribute with the use of same instrument over time. However, this may not be justifiable assumption in nursing because this relies the assumption that the factor being measured has not changed between the measurement points; meanwhile in nursing, many phenomena do change over short intervals. Equivalence compares two versions of the same instrument or two observers measuring the same event. The latter is referred to as inter-rater reliability. Homogeneity addresses the correlation of various items within the instrument. The test of interval consistency examines the extent to which all items in the instrument consistently measure the construct. This is usually tested with Cronbach's alpha. Coefficient value 1.00 indicates perfect reliability. In other words it means that each item in the instrument measured exactly the same thing, whereas a value of 0.00 indicates no reliability. A lower coefficient 0.8-0.9 indicates an instrument that will more richly reflect the fine distinctions in levels of the construct. The high reported

reliability values of an instrument do not guarantee that its' reliability is satisfactory in another sample or with different population, hence the importance of testing instruments with groups of respondent. (Burns & Grove 2009)

Validity means whether an instrument measures what it is meant to measure (Fitzpatrick 1999). There are three types of validity: content, construct and criterion-related validity. Content validity examines the extent to which the method of measurement includes all the major elements relevant to the construct being measured obtained from the literature, representatives of the relevant populations and content experts. Construct validity determines whether the instruments actually measures the theoretical construct that it is meant to measure as well as examines the fit between the operational and conceptual definitions of the instrument. (Burns & Grove 2009) All evidence of content and criterion-related validity contributes to the evidence of construct validity. Criterion-related validity includes predictive and concurrent validity and it provides evidence how well scores on the new measure correlate with other measures of the same construct. Predictive validity provides how the instrument predicts or proposes the future health status of individuals whereas concurrent validity provides how scores on an instrument are correlated with scores on another measure of the same construct. (Kimberlin & Winterstein 2008)

Davis et al. (2006) suggested that in order for any QL/HRQL instrument for children in order to be conceptually strong, it must have the following characteristics: 1) it must have a clear, operationalized definition of QL/HRQL, as this can have major implications for the type of used items; 2) it must be based on a theory of children's QL/HRQL, because of the process by which children reflect on and give voice to their QL/HRQL 3) it must include the important domains of life for children, as this clearly affects the scoring and interpretation of results; and 4) it must have well-constructed items, as wording of the items directly affects the responses given by children. However, above mentioned characteristics are still rare in any available HRQL instrument. In addition, only few available pediatric QL/HRQL instruments are based on an explicit theory of QL/HRQL (Davis et al. 2006).

The HRQL instruments in paediatric oncology are understudied, especially when compared with the adult population (Meeske et al. 2004, Parsons & Brown 1998). The generic instruments are the most common ones to evaluate HRQL for childhood cancer survivors. Disease-specific instruments are not usually appropriate for survivors, because they are designed to capture the immediate effects of diagnosis and treatment rather than issues related to re-integration and the long-term sequel of cancer treatment. (Pearce et al. 2008) At the time of initiation of our study, there were no HRQL instruments specially developed for childhood cancer survivors and parallel instrument for parent-proxy.

Pearce et al. (2008) found in their methodological review of existing scales of measures of QL nine instruments specially tailored to cancer survivors over 18 years of age. Only two of them, Quality of Life in Adult Cancer Survivors (QLACS) and Impact of Cancer

(IOC), appear to have been developed with samples that are representative of a larger population of cancer survivors. However, none of those instruments are specifically developed for childhood cancer survivors.

Recently, Klassen et al. (2010) did a review of the development of available QL/HRQL measures for children with cancer and childhood cancer survivors. They identified 13 questionnaires, out of which six can be used with children on or off treatment and only three were tailored to childhood cancer survivors. However, one of those three measures for survivors was specifically designed for brain tumor survivors, Pediatric Functional Assessment of Cancer Therapy-Childhood Brain Tumor Survivor (Peds-FACT-Brs) and two, Minneapolis-Manchester Quality of Life Instrument (MMQL) and the Quality of life in Children and Adolescents with Cancer (PEDQOL®) had only child-tailored versions available. McDougall and Tsonis (2009) indentified in their systematic literature review (2001-2008) 13 studies where nine different generic instruments were used to assess QL/HRQL in survivors of childhood cancer. Those instruments include the generic instruments PedsQL™ and the SF-36, which are used also in our study (more detailed in section 4.3).

2.2.4 The concept and assessment of fatigue

Fatigue is probably the most common symptom of illness suffered both in acute conditions, and in a range of chronic conditions (Ream & Richardson 1996, Whitehead 2009). Fatigue is a symptom, which may affect a cancer patient's life in both short and long-term, and can cause negative changes in HRQL (Eddy & Cruz 2007, Meeske et al. 2007, Varni et al. 2002a). Despite the fact that significantly less is known about cancer related fatigue in children and adolescents than in adults (Whitsett et al. 2008), it has been shown that fatigue is a significant symptom also experienced by children and young people with cancer (Gibson et al. 2005, McCabe 2009, Meeske et al. 2004, Ruland et al. 2009, Whitsett et al. 2008). The etiology of fatigue in cancer patients is complex, and factors behind it could be physiological factors such as anemia, psychological such as depression, or situational factors such as immobility or problems with relationships. Fatigue has been related to multidimensional sensation which is similar to pain. However, there is a lack of evidence of fatigue as a symptom experienced by survivors of childhood cancer in the adult and pediatric oncology literature. (Langeveld et al. 2000) Fatigue is usually forgotten in the middle of other more obvious late effects of cancer and cancer treatment (Hockenberry-Eaton et. al 1998). Hence, fatigue in childhood cancer survivors might be under recognized, underestimated and even undertreated (Gibson et al. 2005).

The preliminary fatigue studies were conducted during the First World War. At that time, researchers investigated the impact of fatigue on the efficiency and productivity of the industrial workforce. The economic studies were focused on investigating the optimal productivity of the workforce in the military industry. In 1950 the focus was still the same and researchers developed a fatigue list for pilots. The checklist measured the subjective

quality of fatigue in relation to psychomotor tasks. After two decades, investigations spread into other occupational groups like bank workers and industrial shift workers. (Ream & Richardson 1996) According to Hockenberry-Eaton et al. (1999), one of the earliest nursing studies evaluating fatigue in adult patients with cancer was performed in the 1970s.

Nowadays, fatigue is a term that has been used within a broad spectrum of health related disciplines (Ream & Richardson 1996). Fatigue is a widely experienced phenomenon that is present in normal, individuals without any specific health problems, as well as in those with health problems (Davies et al. 2002). Although fatigue is present in healthy persons, its severity and duration are greater in chronic conditions (Jorgensen 2008). In spite of the prevalence of fatigue, it is a complex symptom to be defined or to be understood. In studies of adults, fatigue has been widely noted as a complex phenomenon with multiple causes and dimensions. (Davies et al. 2002) Ream and Richardson (1996) clarified the definition of fatigue for use in nursing thusly: "Fatigue is a subjective, unpleasant symptom which incorporates total body feelings ranging from tiredness to exhaustion creating an unrelenting overall condition which interferes with individuals' ability to function to their normal capacity." Hockenberry-Eaton et al. (2003) defined fatigue as a subjective symptom including physical, emotional and mental aspects, whereas according to Jorgensen (2008) fatigue is a subjective symptom, usually with an elusive etiology. Fatigue can be either acute, chronic or episodic (Hockenberry-Eaton et al. 1999, Hockenberry et al. 2003). Jorgensen (2008) defined chronic fatigue and concluded it to be "fatigue of at least a six-month duration that is not amenable to rest or sleep and has no relation to previous activity. It is a whole-body sensation with major impact on multiple areas of QL, including physical, cognitive, affective and social domains. It is a constant part of the lives of those affected".

All of the above mentioned definitions have been mainly based on research on adults' perspective of fatigue. As in HRQL, there is no shared understanding on the definition and meaning of fatigue from the perspective of children and adolescents. McCabe (2009) describe in her concept analysis on fatigue in children with long-term conditions that fatigue appears to be a subjective experience of tiredness or exhaustion that is multidimensional and includes physical, mental, and emotional aspects. The first study to evaluate fatigue in children with cancer reported that the definition of fatigue varies depending on the developmental level of the study participants (Hockenberry-Eaton et. al. 1998). Hockenberry-Eaton et al. (1999) define fatigue experienced by children (7-12 years old) with cancer as follows "Fatigue is a profound sense of being tired, or having difficulty with movement such as using arms and legs, or opening eyes which is influenced by environmental, personal/social and treatment-related factors and can result in difficulties with play, concentration and negative emotions (most typically anger and sadness)." Davies et al. (2002) identified three different types of fatigue that children with cancer (5-15 years) may experience. Typical tiredness was characterized as a "normal" or expected response to particular events or circumstances that involve the

expenditure of excess energy. The treatment fatigue was often initiated by hospitalization, treatment modalities, or it occurred in the days following discharge. Shutdown fatigue was described as a feeling of sustained or profound loss of energy. It was experienced as an undesirable and negative experience.

Although, like HRQL, fatigue is a subjective symptom and best measured by self-report (Langeveld et al. 2000), there can sometimes be situations where children are not capable or willing to answer themselves. When using objective measures, we have to be aware that patients, parents and staff can define patient's fatigue differently. Hinds et al. (1999) noticed that fatigue was described as increased levels of depressed mood as well as with different physical consequences for children. Adolescents emphasized the dynamic sensation of physical or mental exhaustion. For parents, fatigue was meant as a state of diminished-to-complete loss of energy and decreased ability to participate in social, academic, physical or self-care activities at the child's usual intensity or duration. The healthcare professional's added that fatigue may also mean loss of will and spiritual distress. Despite the differences, parents may provide a different and complementary perspective to their child's own report. (Upton et al. 2008)

Instruments used to measure and describe fatigue also reflect the conceptual confusion of fatigue (Ream & Richardson 1996). Some HRQL instruments may contain questions about fatigue, but usually when fatigue is considered, it is assessed only as a yes-no variable or with a visual analog scale (Eddy & Cruz 2007). Fatigue instruments can differ in their focus, some measuring severity only, and others measuring its duration and impact on a range of functions. Multidimensional fatigue measurement is more informative than a measure of severity alone. (Whitehead 2009) There are few fatigue measures for children and adolescents, but no instrument specifically designed to assess fatigue in cancer survivors before adulthood. Most fatigue instruments are specifically designed for cancer related fatigue in adults. Eddy & Cruz (2007) found in their systematic review nine studies that examined fatigue and its relationship to child's (8-17 years) QL, and seven of those described fatigue in children with cancer, but none for cancer survivors. Due to the fact that cancer related fatigue is discussed in pediatric oncology literature as a symptom that is common but unique to cancer patients (McCabe 2009), one could assume that the referenced instruments are not directly adaptable to childhood cancer survivors. At the time of starting our study, the most suitable existing instrument for this study population was one generic fatigue instrument PedsQL™ Multidimensonal Fatigue scale that has matching child and parent versions (Varni et al. 2002a).

2.3 Previous studies about the late-effects and HRQL of childhood cancer survivors

Cancer itself and different treatment modalities are aggressive, and several physical-, psychological, and social late-effects are reported. Childhood cancer survivors are at a greater risk for multiple problems, ranging from chronic poor health to emotional or

social dysfunction, compared with the normal population (Bradlyn et al.1996, Eiser et al. 2004, Geenen et al. 2007, Parsons & Brown 1998). It is estimated that as much as two-thirds of the survivors of childhood cancer will develop physical and/or psychosocial complications. The severity of late-effects depends on a number of factors such as the type of cancer, its location in the body, the intensity of treatment and the age of the child. (Maurice-Stam 2007) In Pemberger et al. (2005) study on 78 survivors, 33% did not demonstrate any treatment – or cancer related sequelae, 30% showed a single late-effect and 37% had multiple late effects caused by cancer or its treatment. A retrospective cohort study in the Netherlands found that almost 75% of young adult survivors had one or more adverse events and almost 25% had five or more adverse events in their health after childhood cancer. Additionally, 40% of survivors experienced one or more severe, disabling or even life-threatening adverse health event. (Geenen et al. 2007) Some studies have indeed found that HRQL was significantly lower for cancer survivors than for age-, and sex-matched control groups, (Speechley et al. 2006, Stam et al. 2006) and the general population (Grant et al. 2006).

Many studies have highlighted several difficulties and negative ***physical late-effects*** that survivors experience, such as disorders in growth (Schwatz 1999), the development of second malignancies (Cohen et al. 2005, Wallace et al. 2005), osteoporosis (Haddy et al. 2001), infertility (Zebrack et al. 2004) and hypothyroidism (Madanat et al. 2008a). Survivors of childhood cancer may suffer from auditory, cardiovascular, cosmetic, endocrine, gastrointestinal or orthopedic late-effects (Blaauwbroek et al. 2007). Chemotherapy and radiotherapy may have adverse effects on normal tissues and organs like the heart, lungs, bladder, kidneys, breasts, thyroid gland, ears, and liver (Dickerman 2007, Prouty et al. 2006). These effects may manifest months or years after the completion of therapy (Langeveld et al. 2004). Maunsell et al. (2006) stated that significantly fewer survivors than members of control groups reported very good or excellent general health. Survivors were more likely than controls to report having one or more physical health problems, including endocrine, hormonal, cardiovascular, neurologic, and renal problems. There are also studies comparing survivors' HRQL with their siblings' HRQL. For example, Punyko et al. (2007) found that survivors were more likely to report physical impairment than siblings. Survivors were nearly seven times more likely than siblings to have at least one medical condition, and at least six times more likely to report being unable to work or attend to school because of health limitations.

Survivors of childhood cancer face an increased risk for second primary malignancies throughout their lives. This is mainly related to previous radiotherapy but some chemotherapeutic agents are problematic as well. In a registry-based report on a Nordic cohort of 47,697 childhood cancer survivors, the overall risk of second primary malignancies was two to three times greater than cancer risk in the general population. Although survivors of childhood cancers are at increased risk, the absolute risk of second primary malignancies is, quite minor. (Olsen et al. 2009) Within a retrospective cohort of

childhood cancer survivors, Neglia et al. (2001) reported that 1.9 additional cancers will occur for every 1,000 persons. Among Nordic survivors, the second cancer was in 28% of cases located in the brain. However, the location of the second cancer was found to vary by age and gender (Olsen et al. 2009).

Physical appearance and the body image can be affected by the cancer or its treatment (Eiser & Morse 2001a). Female patients treated for ALL are found to be at risk of being obese (Meacham et al. 2005). Survivors may suffer from bodily changes, especially if those are something obvious and visible. Bodily changes such as scars seemed to be a reminder for the survivors' childhood cancer. (Enskär & Berterö 2010)

In contrast to physical late-effects, less emphasis has been put in the literature on ***psychosocial late-effects*** of cancer and cancer treatment in childhood, such as problems in emotional or social adjustment (Lähteenmäki 1999, Stam et al. 2005, Van Dongen-Melman 2000). The lifestyle choices of cancer survivors may be significantly affected by their cancer experiences (Prouty et al. 2006). Survivors seemed to live with parents longer than their peers (Harila 2011, Stam et al. 2005). One of the reasons could be that survivors have the feeling of lack of a secure and healthy future, as well as the feeling of vulnerability, which can interfere with the establishment of new relationships (Ganz 2001). On the other hand, survivors may experience a profound need to socialise with others as they strive to achieve a normal life (Mattsson et al. 2008). Punyko et al. (2007) reported that survivors were less likely than siblings to have completed high school or to have ever worked. In Finland, the survivors seem to have different school-related problems as well. Lähteenmäki et al. (2002) found in their study that cancer patients and survivors required statistically significantly more extra tutoring at school compared with their healthy siblings and healthy members of control groups. They also reported almost three times more bullying than their healthy counterparts. Cognitive impairment has also been reported (Mulhern et al. 2004). For example, it has been found that in leukemia patients, treatment with cranial irradiation or young age at treatment may impair scholastic achievement. However, almost all (97.6%) of Finnish leukemia survivors completed comprehensive school at the typical age. (Harila-Saari et al. 2007) Simms et al. (2002) evaluated prospectively the cognitive, behavioral and social functioning for children receiving SCT and comparing survivors with normative group. The only difference was that the survivors of SCT academic ability were lower than the normative group. They found that children younger than 3 years old may be at risk for decreased cognitive skills.

Long-term effects in adults differ from those experienced in childhood or adolescence as new issues may come up important in their lives (Blaauwbroek et al. 2007). Older survivors may be uncertain about their fertility status (Mattsson et al. 2008, Zebrack et al. 2004), sexual function, marital status and parenthood (Mattsson et al. 2008). It has been reported that long-term survivors of childhood cancer married at lower frequencies compared with peers or sibling group (Harila 2011, Janson et al. 2009, Punyko et al. 2007, Stam et al. 2005, Sundberg et al. 2010). Survivors were found to

be significantly less likely to have children than their siblings (Madanat et al. 2008b). Psychosexual problems are frequent as well. In van Dijk et al's (2008) study, about 20% of the survivors felt limitation in their sex lives due to their illness. Almost 50% of the survivors were seldom or never able to feel that they were sexually attractive. It seems that treatment in adolescence is a risk factor for a delay in psychosexual development. Many survivors have concerns about the health of their offspring. Female survivors tend to have more cancer-specific concerns than male survivors. (Langeveld et al. 2004) In a recent report, survivors and especially female survivors had increased risk for depression, aggression and psychotic tendencies than the general population (Michel et al. 2010). As cancer diagnosis is a traumatic event, some of the survivors may suffer from posttraumatic stress years after their treatment has ended (Hobbie et al. 2000, Meeske et al. 2001). Psychosocial concerns are frequent in childhood cancer survivors. A fear of recurrence and death, adjustment to physical compromise, psychosocial reorientation and accomplishment of developmental tasks may be problematic (Ganz 2001). Survivors have expressed uncertainty about the recurrence of cancer (Langeveld et al. 2004, Prouty et al. 2006) and about having another cancer when they are older (Langeveld et al. 2004). Survivors may also fear the consequences of late-effects of cancer (Prouty et al. 2006).

Langeveld et al. (2000) reported that the adult survivors of childhood cancer who were diagnosed in their adolescence, identified fatigue as a significant side-effect of the treatment. Survivors who were diagnosed before their adolescence identified fatigue as an ailment that had affected their entire life and stated that fatigue has a negative impact on their daily lives. Some reports of young adult childhood cancer survivors have found that fatigue remained the salient aspect of their HRQL (Langeveld et al. 2000, Sundberg et al. 2009, Zebrack & Chesler 2002). Mulrooney et al. (2008) reported that when compared to their siblings, adult survivors of childhood cancer reported more fatigue. In contrast, Langeveld et al. (2003) found less fatigue in adult childhood cancer long-term survivors than in the general population. Meeske et al. (2004) as well as Zelter et al. (1997) reported a similar fatigue level between the ALL survivors and their siblings, as well as their healthy counterparts of the control.

Interestingly, childhood cancer survivors have been reported to have some positive consequences of the disease in their lives as well (Casillas et al. 2006, Langeveld et al. 2004, Mattsson et al. 2008, Pemberger et al. 2005). Some published findings report that childhood cancer survivors have equal (Dijk et al. 2007, Gurney et al. 2007) or even better HRQL than healthy controls or population norms (De Clerq et al. 2004, Eiser et al. 2004, Shankar et al. 2005). In descriptive studies, survivors of childhood cancer have reported positive consequences of the disease with regard to personal values of life, how they relate to others and how they view themselves (Mattsson et al. 2008). Michel et al. (2010) found that childhood cancer survivors have on average less psychological distress than the general population. Traumatic childhood experiences led to an increased appreciation of being alive, as well as to viewing the possible impairments of

their present health status less important (Pemberger et al. 2005). Sundberg et al. (2009) interviewed 246 long-term childhood cancer survivors and asked whether cancer was affecting their current life positively or negatively. At least one negative consequence was reported by 68% of survivors and at least one positive consequence was reported by 53% of the survivors. Most frequently, negative consequences included a variety of physical impairments and limitations of participating in activities. Positive consequences included such things as a more positive view of life, and of themselves. However, the life-threatening experience of cancer is in most cases never forgotten. In many ways, survival enhances appreciation for life, while at the same time reminds survivors of their vulnerability. (Langeveld et al. 2004)

Klassen et al. (2011) found in their systematic review that gender, age at the time of assessment, age at time of diagnosis, ethnicity, type of cancer, relapse status, type of treatment and treatment intensity, the time since diagnosis, various late-effects such as learning problems or hearing loss associated with poorer HRQL. Some aspects of their familiar situation, such as parental health or level of parental education were commonly found to affect HRQL in this population. McDougall and Tsonis (2009) identified in their systematic review that determinants associated with poorer HRQL of adult childhood cancer survivors were female gender, a longer time since diagnosis, older age at diagnosis, certain cancer and treatment types and some socioeconomic factors. One study suggests that a positive correlation exists between self-esteem and higher HRQL among early childhood cancer survivors (with survival periods of more than one but less than five years) (Cantrell & Lupinacci 2008). More severe late effects and fatigue have been reported to be associated with poorer HRQL in childhood cancer survivors (Meeske et al. 2007). Cantrell (2007) found several direct and indirect factors contributing to HRQL in adolescent cancer survivors, such as physical health, perceived level of self-esteem, coping abilities, hopefulness, social support, and overall experiences during treatment. Nonetheless, several studies and systematic reviews demonstrated that female survivors are at a greater risk for a lower HRQL than male survivors of childhood cancer (Cantrell 2011, Hudson et al. 2003, Langeveld et al. 2004, McDougall & Tsonis 2009, Shankar et al. 2005, Zelter et al. 2008, Zelter et al. 2009).

2.3.1 Limitations and shortcomings in previous HRQL studies

There are some limitations and shortcomings in the previously published literature concerning the HRQL and fatigue of childhood cancer survivors.

- There are inconsistent findings in survivors' HRQL in previous studies. It is suggested that those discrepancies might be due to a lack of consensus in using either generic, cancer-specific or cancer survivor's QL/HRQL instruments (Jacobsen & Jim 2011). Due to the current lack of clarity regarding the difference between QL and HRQL (McDougall & Tsonis 2009), there is a mixture of different methodologies such as using QL/HRQL instruments with different definitions and theories (Maunsell et al. 2006). In the literature, there could not be found evidence

to support a definitional or conceptual difference between the used HRQL and QL questionnaires of childhood cancer survivors' studies (Klassen et al. 2011).

- In addition to describing late-effects and HRQL of childhood cancer survivors, there is a growing interest in the literature to find out the determinants associated with HRQL of childhood cancer survivors. Nevertheless, the findings regarding the determinants of HRQL are ambiguous and no uniform model yet exists for those determinants. Only a few studies found the same determinants to be associated with poorer HRQL of childhood cancer survivors (Klassen et al. 2011). Those determinants that have been mostly founded to associated with poorer HRQL of childhood cancer survivors are gender, older age at diagnosis, certain cancer and treatment types, a longer time since diagnosis, more severe late effects and fatigue as well as some family factors such as parental health and level of parental education (Klassen et al. 2008, McDougall & Tsonis 2009, Meeske et al. 2007).

- There are mixtures of studies using different comparison groups, studies lacking a control group, and studies which use siblings as the control group for childhood cancer survivors. In the literature, there are however some disagreements to use siblings as controls. Siblings might have more similar health outcomes to the studied survivors than randomly selected members of a control group (Leiseninger et al. 2009), because of similarity in, for example, socioeconomic status, or family genetics and environmental factors (Zelter et al. 2009). On the other hand, siblings may have suffered from some psychological effects as well because of the cancer diagnosis of a family member (Alderfer et al. 2003, Houtzager et al. 2004). Additionally, there are studies using different childhood cancer populations and different age-groups. The survival time can vary between the studies as well.

- There are studies using either self-assessment or proxy-assessments and in rare cases both. In previous young survivors' HRQL studies, the perspective has often depended on parent-proxy-reporting (Meeske et al. 2004, Schultz et al. 2007, Speechley et al. 2006). Despite that it has been increasingly acknowledged that the child's perspective is different from their parent's perspective. However, parents also experience serious psychological distress related to their child's disease (Lähteenmäki et al. 2004a, Pöder et al. 2008) and this could have an effect on their assessment. In general, parents perceive an illness usually to have more negative consequences than children themselves (Eiser & Morse 2001b). Nevertheless it is strongly suggested that the HRQL should be measured with both the self-assessment and parent assessment. There are few studies which use the parallel HRQL instruments for self-assessment and parent-proxy for childhood cancer survivors. Thus, we need more information about survivors' HRQL estimated by the young survivors themselves, as well as by their parents with generic parallel HRQL instruments.

- Most studies concentrate to find out the HRQL of adult survivors of childhood cancer, and only a few European studies during the adolescence and early adulthood with matched population controls. The school system as well as public health care system in the Scandinavian countries may have some impact on the general HRQL. Thus, we need more Scandinavian reports on how young cancer survivors evaluate their HRQL and compare those with matched population controls.

- There is a lack of evidence of fatigue as a symptom experienced by survivors of childhood cancer in adult and pediatric oncology literature (Langeveld et al. 2000) because fatigue is usually forgotten amongst other more obvious late-effects of cancer and cancer treatment (Hockenberry-Eaton et al. 1998). Previous studies have mainly reported fatigue on adult survivors of childhood cancer and failed to concentrate specifically on children's and adolescents' points of view. There are a limited numbers of long-term follow-up reports on fatigue as a symptom experienced by survivors of childhood cancer, and, to our knowledge, only a few which concentrate on survivors still in their youth. Hence, we need more knowledge about whether fatigue continues after cancer treatment, and whether it has an adverse impact on childhood cancer survivors' lives as well.

With those aforementioned limitations and shortcomings in previous studies, it is difficult to summarize the results of the HRQL studies of childhood cancer survivors. Based on an analysis of available studies, the findings on the HRQL of childhood cancer survivors have not been consistent and more research is needed to reach a greater understanding of the relationship between childhood cancer and its treatment and the HRQL of childhood cancer survivors, as well as to identify survivors in need of aftercare.

3 AIMS OF THE STUDY

The purpose of this study was to evaluate the HRQL of young people that have survived childhood cancer at least four years after cancer diagnosis. Its aims were (1) to increase knowledge and understanding of the relationship between childhood cancer and its treatment and the HRQL of childhood cancer survivors and (2) to identify survivors who need and could benefit from ongoing long-term follow-up, as well as (3) to identify the kind of aftercare childhood cancer survivors' may need.

The more focused tasks in this study were as follows:

1. To describe how children, adolescents and young adults who have survived childhood cancer self-report their HRQL and possible fatigue

2. To compare survivors' HRQL and fatigue scores with the scores of the control group and with those gained from the parent proxy evaluation of children and adolescents aged less than 18 years

3. To analyze whether demographic and/or disease-related factors have associations with survivors' HRQL and fatigue

4. To describe the self-reported items that are causing worries or are rated as best things in the lives of young adults who have survived childhood cancer

4 SUBJECTS AND METHODS

4.1 Subjects of the study and data collection

The total cohort population of childhood cancer survivors aged 11-27 years was identified from the Finnish Cancer Registry (FCR). Eligible survivors had to fulfil the following inclusion criteria; born 1980-1995, treated for extracranial malignancy between 0-16 years of age, survived at least four years from diagnosis, free of cancer at the time of the study, and alive at the end of the year 2006. Information from the FCR was checked and verified by the physicians who had been responsible for the cancer treatment at all five University hospitals taking care of childhood cancer patients in Finland. A total of 852 (448 male, 404 female) survivors met the inclusion criteria. Those parents whose children were below 18 years (N=379) were asked to contribute to the study as well. In order to be eligible to take part in the study, the parents had to live with their child. If both parents lived at the same address, they could decide amongst themselves which one of them would take part in the postal survey.

A general population control group, specifically three control group subjects for each survivor, was selected randomly from the Finnish Population Registry. Three control group subjects were selected, in the interest of getting at least one control group subject for each survivor. Eligible controls had to fulfil the following matching criteria: the same gender, birthday and place of residence than the survivor had, no history of cancer, permanent domestic address and alive at the end of year 2006. If a control group subject with the same birthday could not be found, the criteria for being eligible to be matched with a survivor was widened so that the control group subject need only have been born in the same calendar month, with the second circuit deviation being one previous or later month, the third circuit deviation being two previous or later months, and the fourth circuit deviation to being three previous or later months. The controls needed also to be fluent in the Finnish language since the validated study questionnaires were available only in Finnish. The parents of control children below 18 years of age were asked to contribute to the study as well.

The addresses of the study subjects were collected from the Finnish Population Registry. Data collection occurred between February and July 2007. The questionnaire package contained a cover letter about the study, instructions, informed consent forms, and two age-appropriate HRQL instruments, a fatigue instrument for respondents under 18 years of age and their parents as well as a questionnaire on demographic details. Pre-paid envelopes to return the instruments were provided as well. The questionnaire packages were tailored to the age group of the respondents (see table 2). For respondents under the age of 18, the questionnaire package was sent in the same envelope with the cover letter for parents. Inside the envelope, there were separate questionnaire packages for

the child and the parent. The estimated time to complete the questionnaire package was 15 minutes. Participants were asked to return informed consent forms and coded questionnaires using the envelopes provided. A reminder was sent three weeks after the initial postal package to those survivors and/or parents who had not yet responded. Regarding the control group, the questionnaire package was initially mailed only to the first prospective control group member/parent pair and if they did not respond, the package was mailed to a second and then a third control/ parent, aiming at getting one matched control/parent pair for each survivor/parent pair. The questionnaires were returned directly to the researcher (S.M), at Turku University hospital. All questionnaire package forms were manually coded with numbers and letters, so that child/parent pairs could be kept together. Secretarial help was used in saving the previously anonymous data on Microsoft Excel files. Excel data was imported to SPSS 13.0, and analyzed by S.M with help from a statistical expert (J.M).

4.2 Methodological approach

Figure 2 shows the theoretical framework of this epidemiological and cross-sectional study. In our study, we used Taylor et al. (2008) definition of HRQL, where the young person's unique life characterized in three aspects; the physical, the psychological and social function. The stage of development and the illness trajectory factors are involved in the HRQL, and the significance of those factors may vary at different times in life. The subjective HRQL forms an equation of these aspects and factors. Our study adapted a description from Mullan's (1985) "the seasons of survival", the exception being that in this case, the study concentrated strictly, on the long-term survival of childhood cancer. Assessment of HRQL in this study is focused on self-assessment, but we used parent-proxy for survivors of childhood cancer below the age of 18 years as well. Figure 3 shows the progress of our nationwide cross-sectional quantitative postal survey.

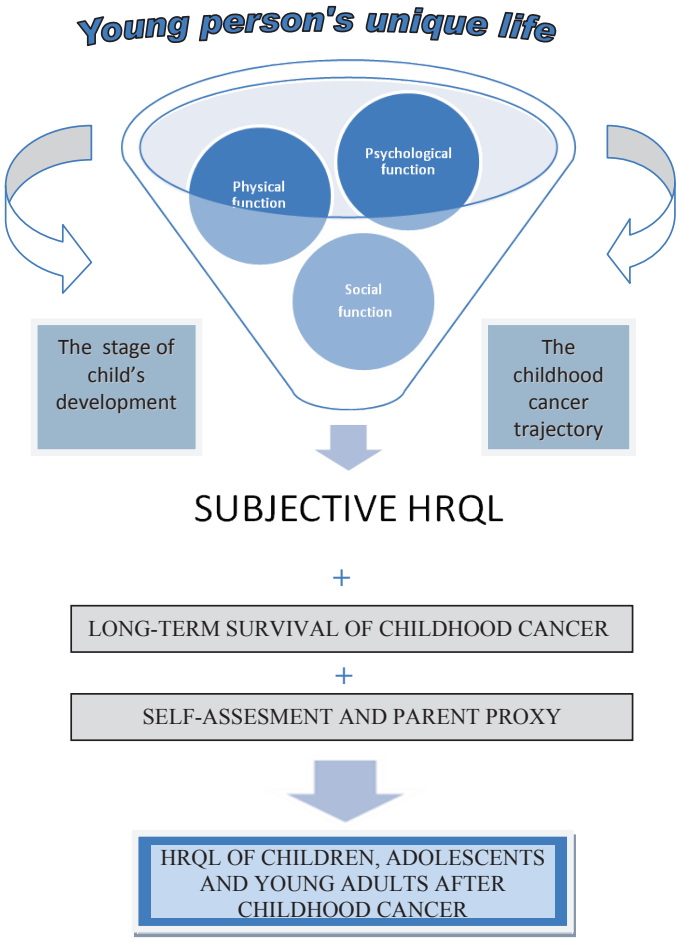


Figure 2. Theoretical framework of the study

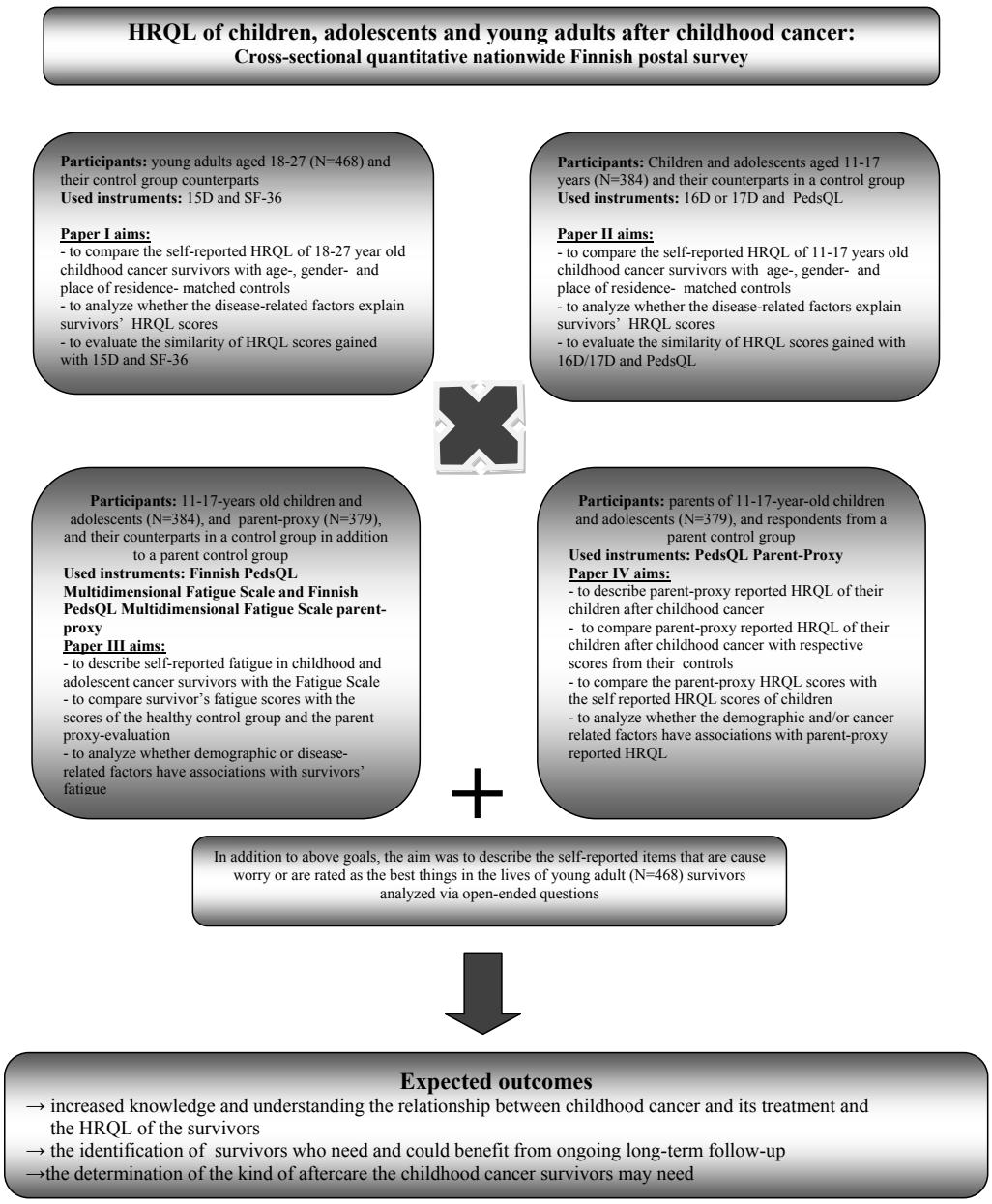


Figure 3. The progress of the Quantitative Cross-Sectional Nationwide Finnish Postal Survey

4.3 Instruments

The instruments were specifically selected to reflect the research questions and objectives. Table 2 shows the used instruments for studied age groups, as well as the dimensions, summary and total scores of the instruments. In this study, only generic HRQL and

fatigue instruments were used. This was in order to compare survivors with their healthy controls and, secondly because the cancer-specific instruments are typically developed only for use during and immediately after cancer treatment. For long-term survivors, there were no specific disease-related instruments available at the time of the study. The selected instruments were brief and suitable for a postal survey.

Table 2. Study instruments for studied age groups, and the dimensions, summary and total scores of the instruments

Age groups	Instrument	DIMENSIONS (Items)	SUMMARY SCORES (Items)	TOTAL SCORE (Items)
11 to 17 years and Parent-Proxy	PedsQL™ 4.0 (Varni et al. 2001, Varni et al. 1999)	Physical (8) Emotional (5) Social (5) School functioning (5)	Physical health (8) Psychosocial health (15)	PedsQL Total Score (23)
11 to 17 years and Parent-Proxy	Multidimensional fatigue scale (Varni et.al 2001)	General fatigue (6), Sleep/rest fatigue (6), Cognitive fatigue (6)		Total Fatigue Score (18)
11-year-old	17D (Apajasalo et al. 1996a)	Mobility (1), Vision (1), Hearing (1), Breathing (1), Sleeping (1), Eating (1), Speech (1), Elimination (1), Discomfort and symptoms (1), Depression (1), Vitality (1), School and hobbies (1), Friends (1), Physical appearance (1), Anxiety (1), Ability to concentrate (1) Learning ability and memory (1)		Total 17D (17)
12 to 17-years	16D (Apajasalo et al. 1996b)	Mobility (1), Vision (1), Hearing (1), Breathing (1), Sleeping (1), Eating (1), Speech (1), Elimination (1), Discomfort and symptoms (1), Depression (1), Vitality (1), School and hobbies (1), Friends (1), Physical appearance (1), Mental function (1), Distress (1)		Total 16D (16)

Age groups	Instrument	DIMENSIONS (Items)	SUMMARY SCORES (Items)	TOTAL SCORE (Items)
≥18-years	15D (Sintonen 1994, 1995, 2001)	Mobility (1), Vision (1), Hearing (1), Breathing (1), Sleeping (1), Eating (1), Speech (1), Elimination (1), Discomfort and symptoms (1), Depression (1), Vitality (1), Usual activities (1), Mental function (1), Distress (1), Sexual activity (1).		Total 15D (15)
≥18-years	SF-36 (Ware et al. 2000)	General health (5), Physical functioning (10), Role physical (4), Bodily pain (2), Vitality (4), Social functioning (2), Role emotional (3) and, Mental health (5) Health transition (1)	Mental component summary Physical component summary	

Self-assessment of HRQL was performed using age appropriate and pre-validated standard measures, which have shown good validity and reliability in international studies: the 15D, 16D or 17D, PedsQL and SF-36 (Apajasalo et. al 1996a, Apajasalo et. al 1996b, Apajasalo et. al 1996c, Reulen et al. 2006, Sintonen 1994, Sintonen 1995, Sintonen 2001, Varni et al. 1999, Varni et al. 2002a). All used HRQL instruments have been already translated and validated in Finland. The 15D, 16D and 17D instruments are based on utility theory and have been developed in Finland and, thus, suitable for a national survey. SF-36 (Reulen et al. 2006, Ware et al. 2000) for adults as well as PedsQL™ (Klassen 2011) for children are the most used generic instruments internationally and both instruments have been recommended for use with a population of childhood cancer survivors (Eiser 2007, Reulen et al. 2006). Also 15D has been used to evaluate the HRQL of adult childhood cancer survivors (Apajasalo et al. 1996c). The Finnish version of PedsQL has demonstrated good validity and reliability in primary school children (Laaksonen et al. 2007). The internal consistency the used HRQL instruments of the study population is reported in the results section. Self-assessment of fatigue was measured with PedsQL™ Multidimensional Fatigue scale. The instrument has shown strong internal consistency reliability (Varni et al. 2002a). The PedsQL™ Multidimensional fatigue scale has not been used in Finland before, but it has previously been tested to evaluate fatigue among cancer survivors more than one year post-therapy (Varni et al. 2002a). Parent-proxy assessment of HRQL and fatigue were measured using PedsQL™ Parent-proxy and PedsQL™ Multidimensional Fatigue Scale Parent-Proxy.

PedsQL™ 4.0, Pediatric Quality of Life Inventory, Version 4.0 and Parent-proxy

The Pediatric Quality of Life Inventory, Generic Core Scales Version 4.0 was used to evaluate the HRQL of the survivors below the age of 18 years. The PedsQL consist of a 23 five-point items with Likert scales ranging from 0 (never a problem), 1 (almost never a problem), 2 (sometimes a problem), 3 (often a problem), to 4 (almost always a problem). It includes a question about how much problems children have been experiencing over the last month. The PedsQL captures four multidimensional scales; physical (eight items), emotional (five items), social (five items), and school (five items) functioning, and three summary scores; physical health summary (8 items), psychosocial health summary (15 items) and total scale score (23 items). The instrument has separate versions for children aged 2-4, 5-7, 8-12 and 13-18 years. The PedsQL™ scale includes concurrent child self-report and parent-proxy report formats (Varni et al. 2002a, Varni et al. 2007). In this study, we used age-appropriate PedsQL™ questionnaires for the age groups 8-12 and 13-18 where the questions are the same in both questionnaires. The scoring and handling of missing items were performed according to the copyright holder. The reversed scores range from 0 to 100 (0-4 scale items transformed to 0-100 as follows: 0=100, 1=75, 2=50, 3=25, 4=0), so that higher scores indicate better HRQL (Varni et al. 1999, Varni et al. 2002a)

SF-36

The SF-36 version 2™ Health Survey, standard (4 week) form was implemented to measure HRQL for ≥18 years old young adults. Eight subscales; general health, physical function, role physical, bodily pain, vitality, social function, role emotional and mental health consist of 36 health attributes. These eight subscales contain two to eight items each, all with Likert scales. All but one of the 36 items (self-reported health transition) is used to score the eight SF-36 scales. This self-reported health transition item (rating of present health compared to that of one year ago) will be analyzed separately. The eight subscales form two component summaries, mental component summary (MCS) and physical component summary (PCS). As suggested by copyright holder, all missing items were calculated if a respondent answered to at least half of the items in a multi-item scale and if not, these were treated like missing respondents. The scoring was performed according to the copyright holder. (Ware et al. 2000) The scoring direction on 10 negatively phrased items was reversed. After that, raw scale scores were computed and transformed to standard scores (0-100 scale), so a higher score indicates better HRQL. This transformation was the norm-based scoring of a standard deviation (SD) of 10 in the 1998 general U.S population (http://www.sf-36.org/tools/SF36.shtml#VERS2).

15D, 16D and 17D

The 15D includes 15 dimensions: mobility, vision, hearing, breathing, sleeping, eating, speech, elimination, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity. (Sintonen 1994, Sintonen 1995, Sintonen

2001). Each of these dimensions has five grades (1-5) of severity in present health status. For example in the mobility dimension:

1. I am able to walk normally (without difficulty) indoors, outdoors and on stairs,
2. I am able to walk without difficulty indoors, but outdoors and/or on stairs I have slight difficulties,
3. I am able to walk without help indoors (with or without an appliance), but outdoors and/or on stairs only with considerable difficulty or with help from others,
4. I am able to walk indoors only with help from others, and
5. I am completely bed-ridden and unable to move about.

The 16D instrument consists of 16 dimensions of HRQL; mobility, vision, hearing, breathing, sleeping, eating, speech, elimination, school and hobbies, friends, physical appearance, discomfort and symptoms, depression, vitality, mental function and distress, which together forms a total 16D score. Like 15 D, each of these dimensions has five grades (1-5) of severity regarding present health status. Using the scoring direction devised by copyright holder (http://www.15d-instrument.net/15d), the original values constructed on to fit a 0–1 scale produced by the valuation system for this age group. The scores range from 0 (worst possible) to 1 (best possible), so that higher scores indicate better HRQL. (Apajasalo et al. 1996b). The 17D consists of 17 dimensions mobility, vision, hearing, breathing, sleeping, eating, speech, elimination, school and hobbies, friends, physical appearance, discomfort and symptoms, depression, vitality, anxiety, ability to concentrate and learning ability and memory. In our study, we used 16D for 12- to 17-year-old survivors and their controls and 17D only for 11-year-old survivors and their controls.

By using the scoring guides which were similar to those of the 15D, 16D and 17D instruments, initially all missing values were replaced and if there were more than three missing values, these answers were treated like missing respondents. Secondly the original values (1-5), were constructed on a 0-1 scale (from 0= died to 1= no problems) by using the copyrights owner's valuation system. Subsequently, a higher score indicates better HRQL. The single index score (0-1) was replaced in same way. The outcome variables in this study were the 15D, 16D and 17D total score and all dimensions. An improvement of 0.03 in the 15D score was found to be a significant amount of HRQL change in the patients (Sintonen 1994, Sintonen 1995, Sintonen 2001). The differences between the scoring of the 15D, 16D, and 17D instruments were that all instruments have own importance weights and within-dimension desirability values. The importance weights and within-dimension desirability values for all these instruments were available by request from copyright holder (http://www.15d-instrument.net/15d).

PedsQL™ Multidimensional fatigue scale and Parent-proxy

The PedsQL Multidimensional Fatigue Scale (Varni et al. 2002a) Finnish version was used to measure fatigue for children under the age of 18. The PedsQL Multidimensional Fatigue Scale captures a 18 item total fatigue (TF) score, which includes general fatigue

(GF), sleep/rest fatigue (SF), and cognitive fatigue (CF). GF includes 6 questions about general fatigue, e.g., "I feel too tired to do things that I like to do", SF includes 6 questions about sleep or rest fatigue, e.g., "I feel tired when I wake up in the morning", and CF includes 6 questions about cognitive fatigue, e.g., "It is hard for me to keep my attention on things". It consist of 18 five-point likert scales ranging from 0 (never a problem), 1 (almost never a problem), 2 (sometimes a problem), 3 (often a problem), to 4 (almost always a problem). It concentrates on how much problems children have been experiencing over the last month. The instrument has separate versions for children of different ages; 5 to 7 (young children), 8 to 12 (children), and 13 to 18 (adolescents) years. The PedsQL™ Multidimensional Fatigue Scale includes concurrent child self-report and parent-proxy report formats (Varni et al. 2002a). The parent-proxy reports were used to assess the parent perception on their child's fatigue and it also exists for children of different ages; 2 to 4 (toddler), 5 to 7, 8 to 12, and 13 to 18 years. This self-assessment instrument has shown good internal consistency reliability for all these different age groups as well as parent proxy (Varni et al. 2002a).

During analysis, the study was score and missing items were addressed according to the method of the copyright holder (http://www.pedsql.org/score.html). After transformation, higher scores (0-100 scale) indicate less fatigue. In this study, we used age-tailored PedsQL™ Multidimensional Fatigue Scale questionnaires for age groups 8-12 and 13-18 years, where the questions are the same in both questionnaires.

Translation and validation process of the PedsQL Multidimensional Fatigue Scale

The linguistic validation adhered to the directions of the linguistic validation of the PedsQL™ - a Quality of Life Questionnaire directions and PedsQL™ Cognitive Interviewing Methodology^{SM} requirements (http://www.pedsql.org/PedsQL-Linguistic-Validation-Guidelines.doc). The linguistic validation of fatigue scale consisted of three phases. All phases in the linguistic validation, including the PedsQL™ Cognitive Interviews, were conducted in close ongoing collaboration with the copyright holder: the PedsQL™ Project Team.

In phase one, two professional translators did the forward translation (English to Finnish) independently. After translations, the researchers reviewed and evaluated the two separate translations and agreed on a single reconciled version of the translation, thus producing the first Finnish version of the PedsQL™ Multidimensional Fatigue Scale. Then, one professional translator translated this first version back into English. The copyright holder reviewed and evaluated that version with the source instrument. A few small modifications (addressing the clarity of the instrument's Finnish diction) of the Finnish version of the PedsQL™ Multidimensional Fatigue Scale were performed. After the required reports to the copyright holder concerning all of the above steps, the PedsQL™ Project Team gave permission to proceed to the second phase. The second phase was the empirical part of the validation process consisting of cognitive interviews. The linguistic validation of patient testing was done by using the respondent

debriefing style of cognitive interviewing (Collins 2003). Firstly, possible problems (for example for the younger children it might be difficult to understand such terms as "physically weak") were identified and noted in the interview. Secondly, an interview protocol was developed according to the copyright holder's instructions to assist in drawing out information from the respondents. Thirdly, a researcher contacted prospective participants for this study by phone and asked whether they would agree to be interviewed. All questioned agreed to participate and the appointment was arranged. The participants were 10 families with children aged 8-12 (n=5) and 13–18 years (n=5) and their parents (n=10). Two participants were boys and eight were girls. The interviews were performed at participants' homes. One parent was male and the other parents were female. Before the interview, the researcher repeated the aim of the study to the participants, reviewed how the interview would be conducted and asked permission to tape-record the interview. The researchers shared that the interview was confidential and anonymous. After filling out and submitting written informed consent forms, the participants completed the questionnaire independently, so that children and adolescents were interviewed separately from their parents. The researcher was present when the participant completed the questionnaire. After the participants completed the questionnaire, questions from the interview protocol were asked in order to increase the level of detail of each respondent's results. Detailed notes were taken during the cognitive interviews. The time spent by each respondent to fill out the questionnaire was also measured. Once the interviews concluded, they were transcribed and analyzed. After the required report to the copyright holder, the PedsQL™ Project Team gave the approval to the Finnish PedsQL Multidimensional Fatigue Scale to be used in practice.

The demographic questionnaires

The socio-demographic factors and cancer related factors were collected with demographic questionnaires. The demographic questionnaires for respondents under 18 included such variables as gender, age at the time of the study, weight, height and age of menarche. The background variables related to school included variables such as current grade level at school, the child's need for remedial education at comprehensive school, and the overall average grade in the latest school marks report in comprehensive school. The overall average grade is calculated from the grades for each school subject (the mean being between 4 and 10, where a higher score indicates better success at school). The age of menarche was included in the questionnaire to evaluate the normality of pubertal development. The background variables related to the family included questions about number of siblings, mother's and father's educational level, and the child's living situation. Adult survivors (≥18-years of age) were also asked about their working and school situation as well as two open-ended questions: "What are the things that are causing worries in your life?" and "What are the best things in your life?" Further, the demographic questionnaire posed questions for all survivors: "Do you have any additional non-cancer diagnosis?" (possible responses; "yes" and "no") and "Do you feel happy?" (possible responses; "yes" and "no"). Supplemental information on

participants' date of birth, mother tongue and home municipality came from the Finnish Population Registry during the matching process. The number of inhabitants of the place of residence was obtained from Statistics Finland (Statistics Finland 2007).

The details of cancer such as the diagnosis, the date of the diagnosis, the date of recurrence, the subtype, treating clinic and data on initial treatment (limited data) were received from the FCR. Additionally, cancer related variables were assessed from children and parents in order to validate the FCR data. The cancer related background variables for survivors were questions relating to their cancer diagnosis, age at diagnosis, length of survival, treatment modality (surgery, radiotherapy, chemotherapy, stem cell transplantation (SCT) including both the autologous and allogeneic transplants, and possible relapses (possible responses; "yes", "no", "do not know"). The FCR data about the cancer treatment were limited, so the information about the cancer treatment was taken from the children and parents.

The demographic questionnaire for parents included the variables of age, gender, educational background, employment status of the parent, family size, and the questions "Do you feel happy?" and "Have you or your family members some diagnosis or illness?" (possible responses to both questions; "yes" and "no"). Demographic questionnaire for the survivors' parents included also the questions about their children's diagnosis, age at diagnosis, treatment modalities (response alternatives; surgery, radiotherapy, chemotherapy, SCT), and relapses (possible responses; "yes", "no", "do not know").

4.4 Ethical considerations

This study was performed in accordance with the Declaration of Helsinki (World Medical Association Declaration of Helsinki 2000, ETENE 2001). The Finnish Ministry of Social Affairs and Health gave permission for the study (1398/900/2006), and the Ethical Committee of South-West Finland Hospital District approved it. Further, the Health and Medical Department Disciplinary Committee of National Health Care, in addition to the pediatric clinic of Turku University Hospital gave permission for the study.

The target group of the study was children who had been seriously ill. For this reason one had to think ethically whether there is more drawback than advantage in the study. The drawback might be that the questionnaire study could remind them of unpleasant memories. The timid pieces of information were not asked in the questionnaires. The study must not prove to cause the respondents excessive emotional strain, especially in such cases where the respondents were handicapped. It is for this reason that the survivors of brain tumors, a group which commonly has a high instance of side-effects caused by cancer and cancer treatments, were not included in this questionnaire study. The identification of the childhood cancer survivors was performed through FCR. Before sending the questionnaire package, the received lists of names were reviewed by the

treating doctors at respective University Hospital Clinics. This procedure was conducted to be sure that the information about the patient's cancer diagnosis in FCR was correct and also because according to the law on public registries (523/1999), one is not allowed to contact anyone based on the registry data. All contact with ill persons is required to be carried out via the treating clinics. It was also checked that no overlapping survivor study being conducted at the same time in Finland. This study was the first nationwide HRQL research among the survivors of childhood cancer. Nationwide data collection aided the researchers in acquiring information about those children's HRQL who have had rare cancer types.

Cover letters and informed consent forms were drafted separately for the survivors and their parents, as well as the control group respondents and their parents. The demographic questionnaires were made separately for the survivors and their controls and also for different age-groups. Written informed consent was obtained from all respondents, as well as their caregivers when the child was under 15-years of age (Medical research Act 2010/794). Survivors, control group respondents and their parents were informed in a cover letter about the purpose of the study, and the name of the study, as well as the names and affiliations of the researchers of the study. All participants could get additional information about the study from a provided contact person (S.M), as well as the names, affiliations and signatures of the doctors at respective University Hospital Clinics. The questionnaire packets were in Finnish only and there were a few survivors, who had other native language than Finnish. This could affect their response, and everyone should have the right to respond in their native language.

The controls' cover letter was formulated similarly as the survivors but from the cover letter clearly appeared that this person is approached particularly as healthy comparison people, whose identification has been performed through the Finnish Population registry. However, there were five parents of control group members, who could not understand the wording of the letter. They called the researcher and asked if their child had had cancer. The cover letter included the study's title which featured the word "cancer", as did the envelopes from University hospital. These details caused an ethical problem. Those parents and children did not understand the meaning of being a part of a study as part of a control group. Surprisingly, there was also one adult survivor who called the researcher (S.M) and declared that she does not have cancer, although according to FCR and clinics, she had had been diagnosed. It is possible that her parents had never informed her. The researcher (S.M) recommended to her to take contact to the doctor at respective University Hospital Clinics, in order to get more detailed information about her situation.

The permission to use the study questionnaires was provided by the copyright holders. The copyright holders' instructions were carefully followed at every stage of the study. The data was analyzed with a statistical expert.

4.5 Statistical analyses

All data analyses were conducted using SPSS (version 13.0). Statistical significance was set to $p<0.05$. Descriptive statistics were calculated for all variables. The HRQL outcome variables for survivors over age of 18 were eight SF-36 instrument sub-scales, MCS, PCS, the 15D and all dimensions of the 15D. The outcome variables for 11-18 year-old survivors were PedsQL emotional, social, and school sub-scales, a physical and psychosocial health summary, the total HRQL score, as well as 16D and 17D total scores and all dimensions of the 16D and 17D. Fatigue variables were the multidimensional total fatigue (TF) score, which included the GF, SF, and CF.

Nonparametric tests were conducted to evaluate the associations of HRQL and fatigue scores with the demographic factors (gender, age at the time of the study, population in the area of residence, living situation, number of siblings, family size, current school, need for remedial education at school, the parents' educational background and employment status, additional non-cancer diagnosis and survivors' and parents' self-reported happiness) for both survivors and control group members and to compare demographic factors between survivors and controls or between the parent-groups (survivor's parent and control's parent). Nonparametric tests were also used to evaluate cancer related background factors between the responding and non-responding survivors. The 16D and 17D instruments were analysed separately, but in the regression model those scores were combined in order to get a larger sample size. Associations between nominal variables were studied using Chi-square tests. Associations between continuous variables and nominal variables were studied using the Mann-Whitney U-test or the Kruskall Wallis test. Comparisons between the two continuous variables were carried out using Spearman's correlation coefficients.

The Mann-Whitney U-test was employed to compare survivor's HRQL and fatigue scores with those of the control group, and to compare survivors' parent proxy scores with those of the controls group's parent proxy. Matched pair statistics were used in survivor-parent pairs but as the results were similar amongst the whole group, comparison between the survivors and control group members, the non-matched statistics were presented in order to avoid losing data. The Wilcoxon Signed-Ranks test was used for comparing different HRQL scores and fatigue dimensions within survivors/control group members/parents. Concordance between the parent-proxy and self-reported HRQL and fatigue was assessed using mean differences and the Wilcoxon Signed-Ranks test. After that, parent and child inter-correlations were analyzed with Spearman's correlation coefficients. Fisher's Z Transformation was used in order to evaluate the possible differences in correlations amongst the total scores of the study groups obtained from PedsQL, MCS, PSC and 15D and 16D/17D.

Hierarchical regression models were developed to analyze associations between clinical characteristics of survivors and outcome variables. Firstly, we analyzed the demographic and cancer related factors as predictors of HRQL and fatigue scores within the control

group and the survivor group (Paper I, II, III), as well as demographic factors of the parent (Paper IV). To investigate which variables might explain the variation in survivors' HRQL and fatigue scores, the researchers added into the models the statistically significant demographic factors (different in separate models) from the univariate analysis, as well as the age and gender of the child and cancer related factors to create a hierarchical regression model. Thereafter, clinical judgment was used to create the order of the regression models (e.g. evaluating the effects of cancer diagnosis before the treatment, and treatment before the length of survival). Cancer diagnoses were mainly entered at the model as separate diagnoses, but some diagnoses were combined in order to get larger sample sizes. The treatment modalities were as follows: surgery alone, chemotherapy alone or with surgery, radiation alone or with surgery or chemotherapy or with both surgery and chemotherapy, and SCT.

In hierarchical regression models, the first category of nominal variables was used as a reference category (see tables 3 in Paper I and II, table 4 in Paper III and table 4 in paper IV). For every five steps, the change in coefficient of determination (R2 change) gained by variables at that step were calculated, as well as the coefficient of determination (total R2), which describes the total explained variation in the scores.

Internal consistency estimates for reliability (Cronbach's alpha) were calculated for survivors and their controls as well as parent proxy versions to find out the internal consistency of the used instruments. Coefficient value ranges in value 0-1. The higher the score, the more reliable the instrument is. (Burns & Grove 2009) The results are presented in section 5.

5 RESULTS

5.1 Characteristics of the responding and non-responding survivors

A total of 474 (male 228, female 246) survivors of childhood cancer participated the study. The response rate was 55.6%. A total of 203 of survivors were under the age of 18 and 271 were aged from 18 to 27 years of age. We received responses from 595 (male 249, female 346) control group members. A total of 266 of controls were below the age 18 years and 329 were aged from 18 to 27 years of age. The survivors' mean age at the time of the study was 18.4 years. The mean length of survival was 12.3 years, and the mean age at diagnosis was 5.5 years. Table 3 shows the demographic and cancer related background factors of childhood cancer survivors and their counterparts in the control group. There were no significant differences found between the clinical characteristics of < 18 years-old respondents (n=203) and non-respondents (n=181) according to the information received from the FCR (see Paper I, table 1 and Paper II, table 1). For ≥ 18 years old non-respondents were more likely to be male 60.4% ($p<0.01$).

Table 3. Demographic and cancer related background factors of childhood cancer survivors and their counterparts in the control group

	Survivors ≥ 18 years (n=271) n (%)	**Controls ≥ 18 years (n=329) n (%)**	**Survivors <18 years (n=203) n (%)**	**Controls <18 years (n=266) n (%)**
Gender				
Male	125(46.1)	125 (38)	103 (50.7)	124 (46.6)
Female	146(53.9)	204 (62)	100 (49.3)	142 (53.4)
Population at the area of residence				
< 50.000	159 (58.7)	180 (54.7)	141 (69.5)	182 (68.4)
50.000-100.000	41 (15.1)	54 (16.4)	21 (10.3)	23 (8.7)
> 100.000	68 (25.1)	95 (28.9)	41 (20.2)	61 (22.9)
Overseas	3 (1.1)	0 (0)	0 (0)	0 (0)
Living situation				
With both parents	52 (19.2)	56 (17)	142 (70.0)	195 (73.3)
With mother or father	29 (10.7)	17 (5.1)	59 (29.1)	61 (22.9)
With someone else	108(39.9)	176 (53.5)	2 (1.0)	10 (3.8)
Alone	82 (30.2)	80 (24.3)	-	-
Siblings				
Yes	244 (90)	311 (94.5)	193 (95.1)	239 (89.8)
No / Not stated	27 (10)	18 (5.5)	10 (4.9)	27 (10.2)
Current level of school / education				
Comprehensive school	0 (0)	0 (0)	83 (40.9)	99 (37.2)
Vocational/ Secondary school	39 (14.4)	51 (15.5)	58 (28.5)	95 (35.8)
University of Applied Sciences	34 (12.5)	46 (14)	-	-

University	34 (12.5)	46 (14)	-	-
Other school/studies	9 (3.3)	10 (3)	5 (2.5)	1 (0.4)
Graduated	73 (26.9)	74 (22.5)	-	-
Graduated, new studies	20 (7.4)	16 (4.9)	-	-
Not stated	62 (22.9)	86 (26.1)	57 (28.1)	71 (26.7)
Need of remedial education at comprehensive school				
Yes	92 (33.9)	86 (26.1)	54 (26.6)	73 (27.4)
No / Not stated	179 (66.1)	243 (73.9)	149 (73.4)	193 (72.6)
Current employment status				
Employed	59 (21.8)	70 (21.3)	na	na
Part time	21 (7.7)	38 (11.6)	na	na
Unemployed	22 (8.1)	19 (5.8)	na	na
Student	108 (39.9)	113 (34.3)	na	na
At military service	6 (2.2)	6 (1.8)	na	na
Maternity leave	9 (3.3)	19 (5.8)	na	na
Retired	6 (2.2)	0 (0)	na	na
Student and employed	12 (4.4)	32 (9.7)	na	na
Something else / Not stated	28 (10.3)	32 (9.7)	na	na
Mother's level of education				
Comprehensive school	45 (16.6)	70 (21.3)	12 (5.9)	11 (4.1)
Vocational / secondary school	69 (25.4)	97 (29.5)	54 (26.6)	63 (23.7)
College-level school	53 (19.6)	57 (17.3)	65 (32.0)	91 (34.2)
University of Applied Sciences	22 (8.1)	26 (7.9)	19 (9.4)	29 (10.9)
University education	40 (14.8)	50 (15.2)	33 (16.3)	41 (15.4)
Other studies	17 (6.3)	19 (5.8)	14 (6.9)	16 (6.0)
Not stated	25 (9.2)	10 (3)	6 (3.0)	15 (5.6)
Father's level of education				
Comprehensive school	60 (22.1)	93 (28.3)	30 (14.8)	34 (12.8)
Vocational / secondary school	86 (31.7)	110 (33.4)	72 (35.4)	83 (31.2)
College-level school	36 (13.3)	28 (8.5)	36 (17.7)	45 (16.9)
University of Applied Sciences	17 (6.3)	19 (5.8)	14 (6.9)	19 (7.1)
University education	34 (12.5)	43 (13.1)	31 (15.3)	45 (16.9)
Other studies	12 (4.4)	12 (3.6)	14 (6.9)	20 (7.5)
Not stated	26 (9.6)	24 (7.3)	6 (3.0)	20 (7.5)
Other diagnosis				
Yes	79 (29.2)	104 (31.6)	51 (25.1)	61 (22.9)
No/not stated	192 (70.8)	225 (68.4)	152 (74.9)	205 (77.1)
Cancer diagnosis				
Leukemia	129 (47.6)	-	111 (54.7)	-
Non-Hodgkin lymphoma	19 (7.0)	-	13 (6.4)	-
Hodgkin lymphoma	30 (11.1)	-	5 (2.5)	-
Neuroblastoma	10 (3.7)	-	15 (7.4)	-
Wilms tumor	16 (5.9)	-	16 (7.9)	-
Gonadal tumor	10 (3.7)	-	7 (3.4)	-
Osteosarcoma	14 (5.2)	-	6 (3.0)	-
Soft tissue sarcoma	11 (4.1)	-	13 (6.4)	-
Retinoblastoma	10 (3.7)	-	6 (3.0)	-
Other /Missing	22 (8.1)	-	11 (5.4)	-

Relapses				
Yes	23 (8.5)	-	16 (7.9)	-
No	248 (91.5)	-	184 (90.6)	-
Missing / Not stated	0 (0)	-	3 (1.5)	-
Treatment modalities				
Surgery only	15 (5.5)	-	7 (3.4)	-
Chemotherapy (alone or + surgery)	123 (45.40)	-	115 (56.7)	-
Radiation (alone or + chemotherapy and/or surgery	101 (37.3)	-	32 (15.8)	-
Stem cell transplantation	31 (11.4)	-	26 (12.8)	-
Not know/ Not stated	1 (0.4)	-	23 (11.3)	-

Na= data not available

A total of 209 parents of children (under 18 years of age) who had survived childhood cancer participated the study. The response rate was 55.1%. Responses were received from 253 control group members' parents. Together 192 survivor/parent pairs and 252 control/parent pairs (n=252, from the same family) participated in the study. Table 4 shows the demographic characteristics of the parents. The mean age of the survivors' parents was 44.1 (SD 5.1) and 44.5 (SD 5.8) for the parents' of controls. Most of the responding parents were mothers. The average family size for survivors was 4.7 (SD 2.4) persons (from 2 to 20 children) and 4.4 (SD 1.7) for control group members (from 2 to 18 children).

Control group members were found more often ($p<0.05$) to have siblings than the survivors in both age groups. The ≥18 years-old control group members needed less remedial education at school ($p<0.05$) than survivors.

The mean height of male survivors < 18 years of age (165cm, SD 13.31) was significantly shorter ($p<0.01$) than that of their counterparts in the control group (170cm, SD 11.63). The mean weight of male survivors (58.7kg, SD 18.34) was lower than that of their controls (61.9kg, SD 16.62), but the difference was not statistically significant. The male survivors ≥18 years of age (176.1 cm, SD 7.3 / 75.7 kg, SD 13.6) were significantly shorter and lighter ($p<0.01$) than their control group counterparts (179.4 cm, SD 6.5 / 81.8 kg, SD 15.9).

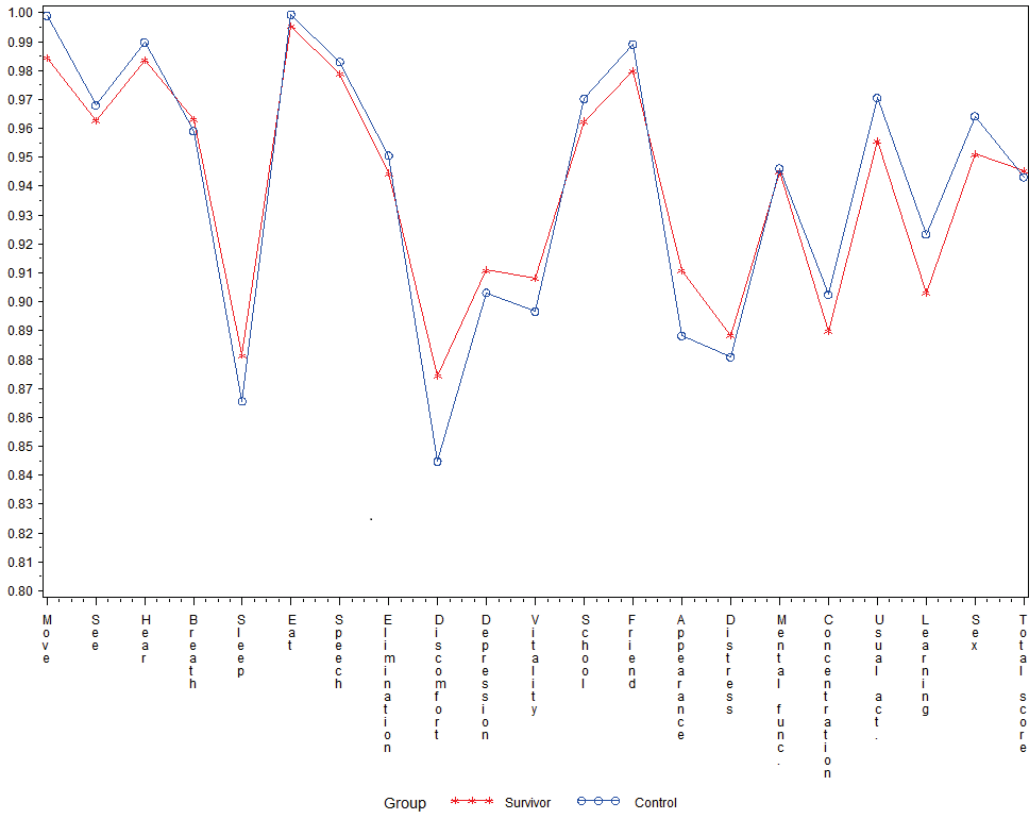
Female survivors < 18 years of age (160.2cm, SD 7.17 / 51.3kg, SD 11.7) were significantly ($p<0.05$) shorter and lighter than their controls (162.6cm, SD 7.20, 53.7kg, SD 9.68). Mean age at menarche was the same 12.3 years for the survivors and the control group members. The female survivors ≥18 years of age (163.6 cm, SD 7.0 / 61.3 kg, SD 13.3) was significantly shorter and lighter ($p<0.05$) than that of female control group members (165.5 cm, SD 6.3 / 63.7 kg, SD 11.9). Mean age at menarche did not differ between the older survivors and their control group counterparts (12.5 years / 12.8 years, respectively) either.

Table 4. The demographic characteristics of the parents

	Survivors' parents (n=209) n (%)	Controls' parents (n=253) n (%)
Gender		
Male	12 (5.7)	13 (5.1)
Female	196 (93.8)	240 (94.9)
Missing	1 (0.5)	0 (0)
Current employment status		
Employed	164 (78.5)	194 (76.7)
Part time	8 (3.8)	14 (5.5)
Unemployed	6 (2.9)	11 (4.3)
Student	3 (1.4)	4 (1.6)
Maternity leave	4 (1.9)	6 (2.4)
Disability pension	7 (3.3)	1 (0.4)
Other	17 (8.1)	23 (9.1)
Other diagnosis in family		
Yes	92 (44.0)	142 (56.1)
No / Not stated	117 (56.0)	111 (43.9)
Self-reported happiness		
Happy	189 (90.4)	232 (91.7)
Not happy/Not stated	20 (9.6)	21 (8.3)

5.2 Self-reported HRQL and fatigue of the survivors

Survivors below 18 years of age gave PedsQL total HRQL mean score 86.08 (SD 11.23), 16D or 17D total mean score 0.95. The survivors scored their physical health mean score (88.43) as significantly higher ($p<0.001$) than their psychosocial health mean score (83.74) with PedsQL instrument. Survivors ≥18 years of age gave total 15D mean score 0.94. They also scored their physical component summary (PCS) score (55.17) as significantly higher ($p<0.001$) than their mental component summary (MCS) score (50.39) with SF-36 instrument. Figure 4 shows the combined 15D, 16D and 17D scores of all of the survivors (n=474) and their control group counterparts (n=595). Altogether survivors scored low (below 0.90) scores in the sleep, discomfort, vitality, distress and concentration dimensions.



* Notice that the 15D, 16D and 17D scales are 0-1.0 and in the figure 0.8-1.0

Figure 4. The combined 15D, 16D and 17D scores between the all survivors and their control group counterparts

Survivors < 18 years of age gave total fatigue mean score 81.07. They estimated themselves significantly ($p<0.001$) more fatigued in the sleep/rest subscale (mean 71.70) than their general fatigue subscale (mean 85.90). Their cognitive fatigue mean score was 85.61. Table 5 shows HRQL and fatigue scores for survivors, control group members, and parents.

5.3 Comparisons between self-reported scores and control scores/parent-proxy

5.3.1 Child and parent concordance with matched child/parent pair

Table 6 shows the PedsQL mean scores and the fatigue scores the matched survivor-parent pairs (n=192), as well as comparisons between the scores of survivors and parent-proxies. The survivors scored a statistically significantly higher total HRQL ($p<0.001$) than their parents' estimates. The same was true with all HRQL subscales and summary scores. There were no statistically significant differences in total fatigue between children

and parent-proxy. The sleep/rest fatigue was the only score where the children estimated a statistically significantly ($p<0.001$) lower score than their parents did.

Table 5. HRQL and fatigue scores for survivors, controls, and parents

HRQL Scores	Survivors <18 years	Controls <18 years	Survivors ≥ 18 years	Controls ≥ 18 years	Survivors' parents	Controls' parents
PedsQL Total (0-100)	86.08	85.17	-	-	80.88	83.08
Physical Health	88.43	87.77	-	-	84.12	85.54
Psychosocial Health	83.74	82.57	-	-	79.15	81.77
- Emotional sub-scale	78.69	75.82	-	-	73.14	73.13
- Social sub-scale	90.74	90.69	-	-	86.25	89.84
- School sub-scale	81.79	81.22	-	-	78.05	82.35
SF-36(0-100)					-	-
MCS	-	-	50.39	47.09	-	-
- Vitality	-	-	64.98	59.48	-	-
- Social Functioning	-	-	90.03	84.54	-	-
- Role-emotional	-	-	88.71	84.07	-	-
- Mental Health	-	-	78.00	73.10	-	-
PCS	-	-	55.17	55.17	-	-
-Physical functioning	-	-	95.76	96.06	-	-
-Role-Physical	-	-	94.2	91.56	-	-
-Bodily Pain	-	-	79.79	75.58	-	-
-General health	-	-	76.01	75.26	-	-
Total 15D (0-1)	-	-	0.94	0.94	-	-
Total 16D (0-1)	0.95	0.94	-	-	-	-
Total 17D (0-1)	0.95	0.97	-	-	-	-
Total Fatigue (0-100)	81.07	78.09	-	-	79.81	81.45
General Fatigue	85.90	83.08	-	-	81.30	81.79
Sleep/Rest Fatigue	71.70	68.38	-	-	75.54	75.75
Cognitive Fatigue	85.61	82.83	-	-	82.61	86.80

MCS = mental component summary, PCS= physical component summary

Survivors' self-reported HRQL and fatigue scores correlated significantly positively with their parents scores (all p values <0.01, Spearman's rho ranging from 0.50 to 0.53 in fatigue scores and 0.41 to 0.55 in HRQL scores). Similarly, as children in both groups, the parents evaluated their child's social sub-scale the highest and emotional sub-scale scores the lowest ($p<0.001$) and their child's physical health higher than their psychosocial health ($p<0.001$).

The control groups rated their total HRQL statistically significantly ($p<0.01$) higher than their parents did. The controls scored their emotional sub-scale ($p<0.05$) and physical summary scores ($p<0.01$) statistically significantly higher when compared with their parent-proxy scores. Also controls' self- reported HRQL and fatigue scores, correlated significantly positively with their parent scores (all p values <0.01, Spearman's rho ranging from 0.43 to 0.51 in fatigue scores and 0.34 to 0.53 in HRQL scores).

Table 6. The PedsQL mean scores and fatigue scores for the matched survivor-parent pairs (n=192), as well as comparisons between the scores of survivor and parent-proxies (n=252)

PedsQL scales	Survivors Mean (SD)	Parent-proxy Mean (SD)	Spearman's rho	Mean Difference
Psychosocial	83.95 (12.10)	80.10 (13.19)	0.43	3.85***
Emotional	79.03 (14.90)	73.62 (16.10)	0.45	5.41***
Social	90.73 (13.54)	87.32 (16.50)	0.41	3.41**
School	82.10 (14.32)	79.36 (16.30)	0.47	2.74*
Physical	88.64 (12.87)	85.09 (17.65)	0.55	3.55**
Total HRQL	86.30 (11.31)	81.83 (13.21)	0.49	4.47***
General Fatigue	86.13 (14.03)	82.07 (15.13)	0.50	4.06***
Sleep/rest Fatigue	71.75 (15.94)	76.04 (16.83)	0.51	-4.29***
Cognitive Fatigue	86.02 (15.69)	83.89 (17.87)	0.53	2.13
Total Fatigue	81.30 (13.14)	80.67 (14.33)	0.52	0.63

* $p<0.05$, ** $p<0.01$, *** $p<0.001$

5.3.2 Comparisons between the survivors and controls

There were no statistically significant differences in the total PedsQL, 16D and 17D mean scores or psychosocial summary scores between < 18 years-old survivors and control group members. However, the survivors scored statistically significantly higher ($p<0.05$) PedsQL physical health mean score (88.43), than the control groups (87.77) did. The survivors rated themselves as significantly less fatigued in SF ($p<0.01$), CF ($p<0.05$) and TF ($p<0.01$) than their control group counterparts did.

Survivors ≥ 18 years estimated their MCS score (50.39) significantly higher ($p<0.01$) than their control group counterparts, as well as all MCS dimensions. Survivors estimated their role-physical ($p<0.05$) and bodily pain mean scores ($p<0.01$) significantly higher than the control groups did. There were no statistically significant differences in PCS, physical functioning or general health between the survivors and the control groups. The survivors yielded a significantly lower (poorer) 15D mobility dimension mean score ($p<0.001$), but on the contrary, a significantly higher (less) discomfort and symptoms mean score ($p<0.01$) than the control groups did. There were no other statistically significant differences in 15D dimensions between survivors and control groups, or for self-reported 1-year health transition.

5.4 Associations between the survivors' HRQL, fatigue and background factors

5.4.1 Associations between the HRQL and fatigue scores and background factors in univariate analyses

Socio demographic variables

Gender did not have any effect on <18-years-old survivors' HRQL. However, the male survivors appeared significantly more fatigued in SF score ($p<0.05$, median 66.67 vs. 75.00) and CF score ($p<0.05$, median 87.50 vs. 91.67) than female survivors. The female

survivors ≥18 years of age yielded significantly lower mean scores in vitality, role-emotional, MCS ($p<0.01$), and in bodily pain ($p<0.05$) than the male survivors with SF-36 instrument. With 15D instrument the female survivors gave significantly lower scores in sleeping, elimination ($p<0.05$), discomfort, vitality, and 15D total score ($p<0.01$), as well as in distress dimension ($p<0.001$) than the male survivors.

Age at the time of the study for <18 years old survivors correlated negatively with levels of PedsQL™ physical health ($p<0.05$, Spearman's rho -0.16). Increased age associated with more fatigue in TF ($p=0.01$, Spearman's rho -0.18) and SF ($p<0.01$, Spearman's rho -0.13). Age at the time of the study did not have an effect on any scores in survivors of at least 18 years of age.

Weight in ≥18 years old survivors correlated positively with levels of 15D total score ($p<0.05$, Spearman's rho 0.14) and discomfort ($p<0.05$, Spearman's rho 0.13). For them, *height* correlated positively with levels of total 15 D ($p<0.01$, Spearman's rho 0.22), discomfort ($p<0.05$, Spearman's rho 0.15), depression ($p<0.05$, Spearman's rho 0.18), distress ($p<0.01$, Spearman's rho 0.22), vitality ($p<0.01$, Spearman's rho 0.23), as well as with SF-36 instrument subscales, physical functioning ($p<0.01$, Spearman's rho 0.16), bodily pain ($p<0.05$, Spearman's rho 0.12), vitality ($p<0.05$, Spearman's rho 0.15), social functioning ($p<0.01$, Spearman's rho 0.17), and role-emotional scores ($p<0.01$, Spearman's rho 0.22). Weight and height were not analyzed for survivors below 18 years of age as, they were still in growing.

Variables related to the school, work, family and living situation

Current school, and working situation did not have a significant effect on HRQL scores. Survivors <18 years who had needed *remedial education at school* scored significantly lower in PedsQL™ psychosocial health (mean 78.27 vs. 85.71, $p<0.01$), total PedsQL™ (mean 81.06 vs. 87.89, $p<0.01$), total 16D (mean 0.93 vs. 0.96, $p<0.05$) and total 17D (mean 0.91 vs. 0.97, $p<0.01$) scores than those who did not need it. They also scored more fatigue in TF ($p<0.05$, median 79.86 vs. 83.33) and CF ($p<0.001$, median 79.17 vs. 91.67) compared to those who had not needed remedial education. *The overall average grade* in the latest school marks report associated significantly positively (grade increase associated with less fatigue) with TF ($p<0.01$, Spearman's rho 0,23), SF ($p<0.05$, Spearman's rho 0,19) and CF ($p<0.001$, Spearman's rho 0,25).

Survivors with *siblings* gave significantly lower scores (mean 83.29 vs. 92.04, $p<0.05$) in PedsQL™ psychosocial health than the survivors with no siblings. *Mother's and father's educational level* did not have any effect on < 18-year-old survivors' HRQL and fatigue scores. *Living alone* indicated lower MCS scores for survivors aged 18 or over. A survivor's *area of residence* did not have a significant effect on HRQL or fatigue scores.

Other background factors:

Survivors <18 years who had *an additional non-cancer diagnosis* had significantly lower scores in PedsQL™ physical health (mean 81.55 vs. 91.01, $p<0.01$) and psychosocial

health (mean 80.28 vs. 84.90, $p<0.05$), as well as total PedsQL™ scores (mean 80.92 vs. 87.95, $p<0.05$) and total 16D scores (mean 0.93 vs. 0.96, $p<0.05$) than those without an additional non-cancer diagnosis. They also scored significantly ($p<0.05$) more fatigued in CF than those who did not have an additional non-cancer diagnosis.

Survivors who *felt happy* at the time of the study reported significantly higher PedsQL™ physical health (mean 89.1 vs. 65.6, $p<0.01$), total PedsQL™ score (mean 89.1 vs. 65.6, $p\leq0.01$) and total 16D (mean 0.96 vs. 0.86, $p<0.05$) scores than those who felt unhappy. Survivor's self-reported happiness did not have significant effect on fatigue scores for survivors <18 years of age. Survivors ≥18 years of age, who *felt happy* at the time of the study reported significantly ($p<0.001$), higher total 15D ($p<0.001$), and MCS scores than those who felt unhappy.

Cancer related background factors:

For survivors <18 years of age, such cancer related factors as diagnostic group, treatment modality, relapse status or age at diagnosis did not have significant effect on any HRQL or fatigue scores. The survival time increase associated with more fatigue in TF ($p<0.05$, Spearman's rho -0.18) and SF ($p<0.05$, Spearman's rho -0.19), but it did not have an effect on HRQL scores.

For survivors ≥18 years of age, age at diagnosis, length of survival and relapse status did not have significant effect on the SF-36 and 15D scores. Osteosarcoma survivors scored significantly lower ($p<0.001$) HRQL in physical functioning, mobility and hearing dimensions than the reference group (survivors of leukemia). Survivors treated with SCT yielded a significantly ($p<0.01$) lower physical functioning score than survivors treated with the reference treatment (surgery only).

5.4.2 Associations of the HRQL and fatigue with background factors in multiple regression analyses

HRQL and background factors in survivors below 18 years of age

Age, gender, parental education, treatment modalities and relapses had no effect on HRQL measured with multiple regression analysis. A one-year age increase at the time of diagnosis indicated statistically significantly lower scores in total PedsQL™ (B=-0.83, $p<0.05$) and PedsQL™ physical summary (B=-1.10, $p<0.05$). A diagnosis of Wilms tumor or neuroblastoma indicated statistically significantly lower total 16D/17D (B=-0.4, $p<0.001$), Total PedsQL™ (B=-6.66, $p<0.05$), PedsQL™ physical (B=-6.92, $p<0.05$) and psychosocial (B=-6.40, $p<0.05$) summary scores than the reference group (leukemia diagnosis). Having no additional non-cancer diagnoses indicated better scores in total 16/17D (B=0.02, $p<0.05$), total PedsQL™ (B=6.55, $p<0.01$) and PedsQL™ physical summary (B=9.39, $p<0.001$). No needed remedial education at school indicated better scores in total 16D/17D (B=0.03, $p<0.05$), total PedsQL™ (B=5.79, $p<0.05$),

and PedsQL™ psychosocial summary (B=7.15, p<0.001). Unhappiness indicated a significantly (p<0.001) lower scores in 16D/17D (B=-0.1), Total PedsQL™ (B=-20.6), PedsQL™ physical (B=-22.7) and psychosocial (B=-18.5, p<0.05) summary scores. All together, the variables in survivors <18 years of age multiple hierarchical model explained, however, only 21-28% of the variation in HRQL scores (see more detailed results in Paper II, Table 3).

Fatigue and background factors in survivors below the age of 18 years

A one-year age increase indicated more fatigue in TF (B=-1.87, p<0.001), GF (B=-1.31, p<0.05), SF (B=-2.74, p<0.001), and CF (B=-1.55, p<0.01). Females were not so fatigued in SF (B=5.36, p<0.05) as males. Sarcoma diagnosis indicated statistically significantly more fatigue in TF (B=-14.28, p<0.01), GF (B=-13.52, p<0.05), SF (B=-14.81, p<0.05), and CF (B=-14.52, p<0.05) than the reference diagnosis (leukemia). Treatment modalities had no effects on <18 years of age old survivors' fatigue in multiple regression analysis. Over 10 years length of survival indicated statistically significantly (B=-6.04, p<0.05) more problems with SF than ≤10 years length of survival. Additional non-cancer diagnosis, overall average grade at the latest school mark report, or self-reported happiness had no effect on fatigue scores. Need for remedial education indicated statistically significantly (B=-6.54, p<0.05) more problems with SF. Better HRQL score indicated statistically significantly (p<0.001) less problems with fatigue in TF (B=0.87), GF (B=0.93), SF (B=0.81) and CF (B=0.86). All together, the variables in the multiple hierarchical model explained 49-65% of the variation in fatigue scores of this age group (See more detailed results in Paper III, Table 4)

HRQL and background factors in the older survivor group

Gender was found to have no effect on *HRQL* in a multiple regression analysis. A one-year age increase (B=0.71, p<0.01) and a one-cm height increase (B=0.21, p<0.05) indicated higher MCS scores. Living alone (B=-3.69, p<0.05), and a one-kg weight increase (B=-0.14, p<0.01) indicated lower MCS scores. Additionally, 15D varied statistically significantly by height (p<0.01). A higher level of education of fathers college level school (B=0.03, p=0.04) or university of applied sciences (B=0.04, p<0.05) indicated higher 15D scores in survivors. Osteosarcoma indicated a significantly lower PCS score (B=-4.41, p<0.05) and Hodgkin's lymphoma better 15D scores (B=0.03, p<0.05) than the reference group (leukemia). The SCT indicated a significantly lower MCS score (B=-7.2, p<0.05) than the reference treatment (surgery alone). The radiation treatment indicated also significantly lower MCS score (B=-4.4, p<0.05) than the reference treatment. Relapse had no effect on HRQL scores. Unhappiness indicated a significantly lower 15D total score (B=-0.11, p<0.001) and MCS score (B=-15.2, p<0.001). All variables in the model explained 33% (p<0.001) of the variation in 15D scores, 36% (p<0.001) of the variation in MCS scores, but only 10% of the variation in the PCS scores. (See more detailed results in Paper I, Table 3)

HRQL and background factors in parent-proxy evaluation for the survivors below the age of 18 years

Female participants in the study had statistically significantly better scores in social (B=7.07, p<0.01), school (B=8.18, p<0.01), psychosocial (B=5.56, p<0.01) and total HRQL (B=5.19, p<0.05) than participating males. Sarcoma diagnosis indicated a statistically significantly lower score in school subscales (B=-22.73, p<0.01), psychosocial summary score (B=-12.62, p<0.05), and total HRQL (B=-12.19, p<0.05). Survivors who had been treated with chemotherapy had statistically significantly lower scores in school sub-scales (B=-16.15, p<0.05), psychosocial summary score (B=-12.60, p<0.05), and total HRQL score (B=-12.28, p<0.05) than survivors who had been treated with surgery only. Those survivors, who had been treated with radiation had statistically significantly lower scores in school sub-scale scores (B=-22.77, p<0.01), psychosocial summary score (B=-14.12, p<0.05), and total HRQL score (B=-14.26, p<0.05) than survivors who had been treated with surgery only. Comparing again with survivors who had been treated with surgery only, the survivors who had been treated with SCT, had statistically significantly (p<0.05) lower scores in school sub-scales (B=-18.76), psychosocial summary score (B=-14.28), and total HRQL score (B=-13.93). Respondents who reported having no other diagnosis than cancer in their family indicated significantly better emotional sub-scale (B=5.72, p<0.05), physical (B=8.61, p<0.01) and psychosocial (B=4.64, p<0.05) summary scores and total HRQL (B=6.02, p<0.01) than respondents who reported their families had other diagnoses as well. Parents' self-reported unhappiness indicated significantly lower emotional sub-scale score (B=-13.97, p<0.01), physical (B=-10.54, p<0.05) and psychosocial (B=-8.62, p<0.01) summary scores and total HRQL (B=-9.29, p<0.01) than if they felt happy. All variables of the regression model explained 11-20% of the variation of the HRQL scores, where emotional (14%, p<0.01) and school sub-scale (21%, p<0.001), physical (15%, p<0.01) and psychosocial summary score (18%, p<0.01), as well as total HRQL (20%, p<0.001) changes were statistically significant. (See more detailed results in Paper IV, Table 4)

5.5 Self-reported worries and best things in the lives of young adult cancer survivors

There were 218 survivors over 18 years of age who answered the demographic questionnaire's open question: *"What are the things that are causing worries in your life?"* There were altogether 396 separate expressions from survivors to this question. 297 control group members yielded 546 separate expressions. The answers to this question were classified into ten different categories which were related to physical health, mental health, social environment, economic situation, education, working place, global matters, future, cancer, other things, and cancer related worries. Twenty survivors wrote that they did not have any worries. Table 7 shows the expressions of young adult survivors and their control group counterparts about issues that cause worry in their lives, as well as examples of survivors' authentic expressions in each group.

Table 7. The expressions of young adult survivors (n=218) and their control group counterparts (n=297) about issues that cause worry in their lives, as well as examples of survivors' authentic expressions in every category

Worries	Survivors' expressions (n=396)	Controls' expressions (n=546)	Examples of survivors' authentic expressions
Physical health (such as own physical health, diet and weight, pregnancy)	**73 (18.4%)**	**45 (8.2%)**	*"A cataract and the upcoming surgery"* *"My blood results. When the blood test results jump around - not much else."* *"The progress of epilepsy (now under control with medication)."* *"Fatigue possibly from hypothyroidism (this is under investigation)."* *"Testicular anomaly (no malignant change, acquired or congenital).* *"Problems with the fit of the prosthetic leg"* *"The health of the bones of my feet, my knees and one hip have started malfunctioning and started to show signs of wear. I now take Glucapal 400 mg to see if the treatment would slightly slow down the degeneration."* *"When I read a few months ago about retinoblastoma and it said what illnesses can appear for those who have it in both eyes."* *"The preservation of health, although I am fit and healthy right now, I still sometimes wonder if the situation will remain good."*
Mental health (such as own mental illness/symptoms, stress)	**18 (4.5%)**	**13 (2.4%)**	*"I regularly go to therapy because of depression and anxiety due to a traumatic experience."* *"I have also been depressed, and I don't really know what the cause is or what I can do to help."* *"Can I ever be truly happy the way I was before?"* *"Furthermore, I suspect I have an attention disorder."* *"About my mental state now and then, life's meaninglessness and grayness."* *"Can I ever come out of the current darkness and what if I go back to it?"* *"I got moderately depressed about a year ago for which I took some medication, but now I'm without the medicine and feeling better, perhaps I get a mild depression, but it's under control and I am aware of it."* *"Bi-polarity."*
Social environment (such as social relationships, loneliness, partnership, relatives' well-being)	**53 (13.4%)**	**102 (18.7%)**	*"I am worried that I'm alone all the time. I would like to also get many new friends. "* *"Living alone, I have no real friends or support."* *"Outside of work, relationship issues are weighing on my mind."* *"The relationship hasn't been going well recently and making decisions is difficult."* *"Also the health and life situations of my family and those close to me are worrisome."* *"I have also been paying attention to my daughter, worrying about her health and I am afraid I'll lose her (the imagination does tricks)"* *"My mother's alcohol consumption and health because she is dating an alcoholic with a personality disorder. I am also worried about my sister's condition since she lives with my mother so she can't be well either, I am in low spirits because eight of my friends have died within a year, but, considering the circumstances, I am doing well."*
Economic situation	**42 (10.6%)**	**79 (14.5%)**	*"The financial situation"*
Education (such as getting into education, school success, choice of a profession, lack of education)	**57 (14.4%)**	**89 (16.3%)**	*"Studying. I'm in the third year of medical school and it is really tough and last week was the worst of the year."* *"I'm worried that I won't be able to start studies again next fall. The reason is that I can't get up in the morning."* *"I am worried about finding my own field. I'm not sure what field I would like to study though I have been accepted to study. But now I don't have anything I am really worried about."*
Working place (such as getting job, general working issues)	**54 (13.6%)**	**90 (16.5%)**	*"Now that high school is finished, the future is uncertain. I don't know where I am and how I will manage in four months' time."*

Global matters	**10 (2.5%)**	**38 (7.0%)**	*"Entering the rat race."* *"Universal issues such as global warming and the threat of bird flu mutating to become contagious from one person to another."*
Future	**27 (6.8%)**	**59 (10.8%)**	*"Hard to say, I guess it might be a little about what the future will bring because I've already had some of those not-so-nice experiences."*
Other things (such as driving license, baldness, time management)	**17 (4.3%)**	**31 (5.7%)**	*"It seems that I care about everything too much, everything should all the time be perfect and not just almost."*
Cancer related worries - Inheritance - Late-effects - Fertility - Relapse	**45 (11.4%)** 7 6 15 17	-	**Inheritance:** *"That my cancer can be inherited. My oldest daughter (3) has the same cancer and the risk is 50% for every child that's born."* *"How real/unreal it is that one of the children might get leukemia or some other cancer just because I've had it."* *"My girl's health. The girl is healthy enough, but sometimes I wonder if she can get, for example, leukemia more easily because I've had it. I have no knowledge of whether the disease is hereditary, but I have heard that leukemia does appear in my family."* *"It being hereditary was entirely new to me. Everyone in my family was studied, but nobody else had anything."* **Late-effects:** *"Do the treatments affect the appearance of other illnesses, namely, is there a high risk of another disease or of deteriorating health?"* *"I'm also concerned about the durability of the heart since it has always been considered that heart failure, etc. could possibly ensue."* *"Have the treatments, for example, "destroyed" some organs."* *"My main concerns are the daily things, but I don't have any great concerns. Disease-related issues are very distant, but sometimes something like intermittent pain can cause a scare. Restrictions on movement are, however, present every day, for example from exercise that is too strenuous. Certain sports are unsuitable, and sometimes bothersome situations happen when I can't participate in the same way as the others."* *"I am still ill often (at least five common colds a year). I've been ill so much from the time the cancer treatments ended. Doctors do not say anything at all about this. I would be grateful if I got some information (if it is available) on how normal this is and if my resistance will build up over the years."* **Fertility:** *"In recent weeks the issue of infertility has surfaced. I received MOPP chemotherapy so I knew that my fertilization ability could be impaired, and I know from exams that I cannot have children of my own. The issue is more difficult for my wife than me, but it does reflect into my own life, of course, but in a new way. I first examined the issue in spring 2006; just last week it was finally confirmed. Society should, in cases like mine, at least pay for the examination, but otherwise I am not really worried about anything, not even death. I feel that when the day finally comes, we're even, taking it one day at a time."* *"In the future, my only concern is the potential impact of the treatments on fertility and because of that, on the impact it'll have on starting a family."* **Relapse:** *"The potential of a cancer recurrence. I don't dare use birth control pills or other contraceptives that affect hormones because I'm afraid they might contribute to the onset of cancer. I cannot work/deal with this issue normally. I don't want children: one of the reasons is the fear of this disease being inherited. Breast cancer (I have had radiation therapy in the chest area)."* *"The most serious concern, however, is that the disease will recur, as has happened before."* *"Also, when you need to go for a medical follow-up, old memories come back to mind so strongly, and you always fear the worst. (If there is a change in the results)."* *"Of course I am also worried of the appearance of some spot that is malignant."* *"That is it still possible to get sick. Small hypochondria ... "* *"Of course I still think of whether the cancer will recur. In a way what I'm afraid of is that I would have to stop my normal routines and return to the hospital, stop studying, etc."*

Table 8. The expressions of young adult survivors (n=239) and their control group counterparts (n=320) about the things specified as being the best in their lives, as well as examples of survivors' authentic expressions

Best things	Survivors' expressions (n=776)	Controls' expressions (n=983)	Examples of survivors' authentic expressions
Physical health (such as own physical health, relatives health)	**70 (9.0%)**	**61 (6.2%)**	*"Health really is a great thing."* *"When I get healthy, it'll be the best thing in my life at that moment."* *"I'm healthy; I can walk without a cane."* *"Also it's being healthy and finally able to enjoy life and live to the fullest. I'm also happy that my health is good and I recovered from my illness. I feel healthier than ever before. I can do and enjoy things without my previous illness limiting me. Exercise is an important driving force that I wouldn't want to lose. Recovering from cancer gives me self-confidence and a belief in being able to cope with future challenges; it has helped me cope with many difficult issues. On the other hand even small things make me happy."* *"Everyone in the family is healthy."* *"General well-being."* *"Being able to live a full life despite being regularly ill as a child."*
Mental health	**30 (3.9%)**	**4 (0.4%)**	*"I am happy with my own life. I feel a sense of calm satisfaction every day."* *"In general, life is much better than a year ago. Although feelings and thoughts are like a roller coaster ride. Life seems good for the first time in ages."* *"It's that I am happy and feel comfortable being myself."* *"I know how to live day by day and I don't want to think too much about the future."*
Social environment (such as family and social relationships, own child or future child, relatives and familiars, girl/ boyfriend, wife/ husband, friends, home, hobbies)	**494 (63.7%)**	**600 (61.0%)**	*"I also have a very close relationship with my mother which I am grateful for. My brothers are also important."* *Children. The greatest thing is that the children are healthy and feel well."* *"My future child gives me strength."* *"Friends who help you cope and encourage you; my therapist belongs in this group."* *"The fact that I get to spend time with friends."* *"Fun school friends and a good spirit both at school and during my free-time with the same friends. I have a few really good friends with whom I can share things and can talk about anything. "* *"A boyfriend, who loves, cares for and supports me."* *"A relationship is definitely the best part of my life. I am happy that I have found a person who can accept the marks left by the disease. "* *"My home is my safe haven and retreat."* *"The motorcycle and the car that I can fiddle around with."*
Economic situation	**7 (0.9%)**	**24 (2.4%)**	*"A good financial situation"* *"A moderately secure income"*
Education (such as studies, school, graduating)	**52 (6.7%)**	**60 (6.1%)**	*"At the moment, the best thing in my life is studying and all that it involves."* *"The matriculation exams are behind us and I am passing them, so we will be celebrating."* *"I will graduate from a polytechnic school in June, so I can finally get my life started."*
Working place (such as good working place, success at work)	**54 (7.0%)**	**80 (8.1%)**	*"Being successful at work."* *"I got a job for the whole summer in a place that I like it and the pay is good."*
Religion	**6 (0.8%)**	**11 (1.1%)**	*"Faith in Jesus."* *"The Bible course, which I like very much."*
Other things (such as weather, life itself, freedom, own pet)	**63 (8.1%)**	**143 (14.5%)**	*"Everything is the best!"* *"I can live a normal life with family and friends."* *"That I can hope that my life will continue to improve in the future. I am also glad that I have learned to become independent and have been able to move away from home."* *"Postcards from abroad."* *"I know how to take things (usually) positively."*

To another demographic questionnaire's open question: *What are the best things in your life?"* - altogether 239 survivors and 320 control group members replied. There were altogether 776 expressions from survivors and 983 from control group members'. Answers to this question were classified into eight different categories which were related to physical health, mental health, social environment, economic situation, education, working place, religion and to other things. Table 8 shows the expressions of the young adult survivors (n=239) and their control group counterparts (n=320) about the things specified as being the best things in their lives, as well as examples of survivors' authentic expressions in every category.

5.6 The internal consistency of the used HRQL and fatigue instruments

Table 9 shows the internal consistency (Cronbach´s alpha) of the used HRQL instruments in our study population. Table 10 shows the consistency of the PedsQL™ Multidimensional Fatigue Scale (Cronbach´s alpha) in our study population.

Table 9. The internal consistency (Cronbach´s alpha) of the used HRQL instruments in our study population

HRQL	Survivors	Controls
Total 15D	0.82	0.81
Total 16D	0.77	0.78
Total 17D	0.85	0.82
SF-36 MCS	0.86	0.89
SF-36 PCS	0.69	0.71
Total PedsQL	0.91	0.90
PedsQL Psychosocial health	0.89	0.88
PedsQL Physical health	0.83	0.75

Table 10. The internal consistency of the PedsQL™ Multidimensional Fatigue Scale (Cronbach´s alpha) in our study population

Multidimensional Fatigue Scale	GF*	SF*	CF*	TF*
SELF-REPORT				
All survivors (n=203)	0.86	0.70	0.91	0.91
Survivors from 11 to 12 years (n=57)	0.86	0.74	0.92	0.92
Survivors from 13 to 18 years (n=146)	0.86	0.66	0.90	0.90
All controls (n=266)	0.86	0.58	0.89	0.89
Controls from 11 to 12 years (n=73)	0.80	0.57	0.82	0.84
Controls from 13 to 18 years (n=193)	0.86	0.54	0.90	0.89
All self reports together (n=469)	0.86	0.64	0.90	0.90
PARENT-PROXY				
Survivors' parents (n=209)	0.86	0.82	0.93	0.93
Controls' parents (n=253)	0.83	0.71	0.90	0.90
All parents together (n=462)	0.85	0.77	0.92	0.92

*GF= General fatigue, SF=Sleep/rest fatigue, CF=cognitive fatigue, TF=Total fatigue

6 DISCUSSION

6.1 Discussion of results

Modern methods of treatment, the centralization of care, unified treatment protocols and clinical trials have contributed to improvement in survival rates of childhood cancer (Maurice-Stam 2007). However, it is worthwhile to notice that childhood cancer experience does not stop just by virtue of surviving (Casillas et al. 2006). Children and their families may have accepted that cancer itself and its' life-saving treatments have left their own scars in terms of compromised physical, psychological and social functioning (Eiser 2004), and the experience of having had cancer as a child continues to affect survivors later in their life (Prouty et al. 2006). The purpose of this Finnish total population cohort study was to evaluate the HRQL of young people who have survived of childhood cancer at least four years after cancer diagnosis. It is important that health care professionals are aware about childhood cancer survivor's HRQL and the relationship between disease and its treatment and HRQL in order to anticipate survivors' needs for information and education. This understanding could also help health care professionals to develop more efficient psychosocial aftercare for childhood cancer survivors in the future, so that good evidence based physical and psychosocial care could be provided to support and enhance survivor's HRQL. The majority of the young survivors of childhood cancer had a good HRQL after their cancer experience. However, there were subgroups of survivors who had poorer level of HRQL than the others.

The self-reported HRQL and fatigue of children, adolescents and young adults

Our first aim was to describe how children, adolescents and young adults who have survived childhood cancer self-report their HRQL and possible fatigue. According to our results, the most of the Finnish childhood cancer survivors evaluated their HRQL being good and very near that of the controls. This result was in line with previous studies where survivors have reported equal or higher HRQL than their controls or general population (Apajasalo et al. 1996c, De Clerq et al. 2004, Dijk et al. 2007, Gurney et al. 2007, Langeveld et al. 2004, Shankar et al. 2005). However, there are studies, where survivors overall have lower HRQL scores than their controls (Grant et al. 2006, Speechley et al. 2006, Stam et al. 2006). Although survivors in general have reported more physical health problems than their controls or expressed a lower HRQL than their matched comparison group, the HRQL differences between survivors and controls have usually been small, and for the most part maybe not clinically important (Maunsell et al. 2006, Stam et al. 2006).

Due to the fact that HRQL is very subjective, making interpretations about the HRQL scores is difficult. However, it seems that studies using the same HRQL instruments give the same kind of results about HRQL of childhood cancer survivors regardless of

the used control groups. Hence, it seems that some survivors have managed to grow and develop in positive ways in spite of their cancer experience like the majority of our study population (Casillas et al. 2006, Langeveld et al. 2004, Mattsson et al. 2008, Pemberger et al. 2005, Zeprack & Zeltzer 2003), but there are subgroups of childhood cancer survivors who have poorer level of HRQL.

Our results show that survivors of childhood cancer in general do not suffer significant fatigue when comparing with their controls. Actually, survivors expressed equal amount or less fatigue than their controls did. Zelter et al. (1997) and Meeske et al. (2004) reported similar fatigue level between ALL survivors and their controls. Mulrooney et al. (2008), on the other hand, reported that adult survivors of childhood cancer reported more fatigue compared to sibling controls. Varni et al. (2002a) found that the survivors over 12 months off treatment had more fatigue than the healthy population control group when evaluated by parent-proxy, but this difference was not seen in child self-report in the same study. However, it should be noted that the prevalence of fatigue among healthy adolescents is quite high (Mears et al. 2004, ter Wolbeek et al. 2006). This was seen also in our study. Very alarming was that many Finnish children and adolescents seem to suffer especially from sleep related fatigue. Survivors suffered similarly most about sleep related fatigue. During the time of adolescence, sleep regulation, behaviour and timing of the day schedule usually change substantially. Many adolescents obtain insufficient sleep and it has been found that sleep deprivation is associated with increased risk for accidents and injuries as well as has negative effects on control of behavior, emotions and attention. (Carskadon et al. 2004, Dahl & Lewin 2002, Wolfson & Carskadon 1998) Insufficient sleep might be caused by early starting time of school days, social pressure, academic workload or hormonal changes and puberty itself. It has been shown that poor sleep quality and insufficient sleep are associated with worse school performance. (Dewald et al. 2010) Hence, more attention should be paid to the sleep regulation, behaviour and habits of children and adolescents in order to secure normal development and growth for them.

The positive results of self-report with generic fatigue instrument do not necessarily mean that a survivor is not fatigued. Survivors may have developed different unique strategies to deal with fatigue during their active cancer treatments, (Davies et al. 2002) which the control group members may not have had. Those strategies of survivors can help them to move on after cancer and could be useful in dealing with possible fatigue later in their life. On the other hand, survivors may have decreased their inclination to report fatigue (Perikardis et. al. 2008) or may underestimate their fatigue after having got along with cancer related fatigue (Sundberg et al. 2008). Additionally, survivors may have adapted (Langeveld et al. 2000) or have become tolerant to their fatigue level and feelings of fatigue.

Comparisons of the survivors' HRQL and fatigue levels with those of their controls and with parent-proxy

Our second aim was to compare survivors' HRQL and fatigue scores with the scores of the control group and with parent proxy evaluations. We found that, overall, survivors

had equal or better HRQL and they suffered similarly or from less fatigue than their controls by the results gained with all the used instruments. In our study, the only dimension where the survivors as a group scored poorer than the controls was the 15D mobility dimension. This was in keeping with previous reports about survivors' lower physical functioning compared with their controls (Blaauwbroek et al. 2007, Zelter et al. 2008). Surprisingly, however, in our study survivors scored their physical health higher than their psychosocial or mental health.

Our finding, about survivors scoring their HRQL statistically significantly higher than their parents evaluated it, is in keeping with previous findings stating that parents tend to estimate the HRQL of their children poorer than children themselves (Johnston et al. 2003, Eiser & Morse 2001b). It has been earlier shown that parents perceive an illness like cancer to have more negative consequences than children themselves (Eiser & Morse 2001). In general, our results showed, however, that the parent-proxy evaluations were mostly in line with their children's self-reports, as the mean differences in given scores were quite small and probably not clinically meaningful. Interestingly, the parents evaluated, similarly with the children, their child's physical health higher than their psychosocial health as well as social sub-scale the highest and emotional sub-scale scores the lowest. In addition, it seemed that survivors' parents were able to estimate their children's fatigue broadly similarly as the children themselves. The sleep/rest fatigue was the only score where the child gave statistically significantly lower estimates than their parents did. This meant that children felt themselves getting less rest than their parents estimated. The reason for this discrepancy could be that the parents are not totally aware of their child's sleeping behavior. The children stay in their rooms e.g. playing computer games or spending time in the social media even though the parents believe them already sleeping.

Although it is strongly suggested in the literature, that the HRQL as well as fatigue should be measured with both self-assessment and parent-proxy whenever possible (Eiser et al. 2001b, Felce & Perry 1995, Varni et al. 2002a), there are discussions about whether the ratings of children and parents have agreement or not. In our study, children's self rated HRQL and fatigue scores correlated significantly positively with the scores given by their parents. Previous studies have shown that agreement is better between parents and chronically ill children compared with parents and their healthy children (Eiser & Morse 2001, Upton et al. 2008). In our findings we couldn't confirm this statement, because the controls' correlations with their parents were approximately the same as the survivors' correlations with their parents. Our findings are in line with previous studies telling that there are greater agreement for observable functioning (e.g. physical HRQL) and less for non-observable functioning (e.g. emotional or social HRQL) (Eiser & Morse 2001b). However, in PedsQL the majority of items (18 of 23) deal with issues about what a child can do, rather than how she/he feels. Thus, it may be that our moderate agreement is due to the fact that there were so many observable items in our instruments. (Upton et al. 2008)

This kind of assumption about the agreement between children and parents leads to an interpretation that if the agreement between the child and proxy rating is poor then the measure is in some way inadequate (Eiser & Morse 2001b). It has increasingly been acknowledged that the child's perspective is different from her/his parent's perspective (Eiser & Morse 2001b). There can be several reasons for that. Firstly, the parent reports may be subject to inflation due to parental stress (Lindahl Nordberg & Boman 2008, Meeske et al. 2004). For example, Eiser & Eiser (2000) found out that mothers with poorer QL reported also more problems in their child's QL. This was seen also in our study, as the majority of proxy-reports were made by mothers and unhappy parents estimated their child's HRQL poorer than the happy parents. Or vice versa, the child's physical or psychosocial unhealthy behavior could affect the parent's happiness. Secondly, the parents could also be influenced by their children's previous cancer related fatigue as discussed earlier. Thirdly, children or adolescents may want to hide their symptoms from those close to them, and if a child or adolescent feels (or rates) her/his symptoms as "normal", she/he probably do not always seek help for them (Woodgate 2008). Lastly, Eiser and Eiser (2000) have pointed out that the caution is needed in interpreting parental reports as close reflections of young people's subjective experiences. A mismatch could arise from mothers having imperfect knowledge of relevant events in their child's life, especially outside the home. (Eiser & Eiser 2000) Thus, the question should not always be who is right but what does each evaluation contribute to our understanding of children's HRQL (Parsons et al. 1999). Hence, agreement or not, the parents could give another perspective of the child's HRQL (Upton et al. 2008, Varni et al. 2007).

Associations between survivors' HRQL, fatigue and background factors

According to our third aim, we analysed further demographic and disease-related factors to find out whether there were any special groups of survivors who had a lower HRQL. There were, however, only few demographic and disease-related factors that associated with HRQL scores. The demographic factors that associated with poorer HRQL were female gender, greater weight, living alone, need of remedial education, an additional non-cancer diagnosis, survivors' with siblings, and self-rated unhappiness. Like in several studies, our results showed that female survivors' ≥18 years of age had a substantial risk of developing adverse HRQL in many different dimensions compared to male survivors (Alessi et al. 2007, Blaauwbroek et al. 2007, Cantrell 2011, Hudson et al. 2003, Langeveld et al. 2004, McDougall & Tsonis 2009, Shankar et al. 2005, Zelter et al. 2008, Zelter et al. 2009). This kind of result has not been reported only with childhood cancer survivors, but also in the general healthy population (Langeveld et al. 2004, Maunsell et al. 2006). Similarly, in our study, the female controls estimated their HRQL inferior than control males did. Interestingly, however, gender showed no effect on survivors' self-rated HRQL in our multivariate analyses.

Our results showed that the anthropometric measures might have indirect influence on survivors' HRQL, because childhood cancer and its treatment may affect the physical development of the survivors. Height increase indicated higher MCS score, whereas

weight increase indicated lower MCS score. Mean height and weight of survivors were significantly lower than those of controls. In contrast there are some studies reporting survivors' overweight (Meacham et al. 2005, Oeffinger et al. 2003). Interestingly, Janson et al. (2009) reported that childhood cancer survivors with short stature were more likely to never marry. Also living alone indicated lower MCS scores for ≥18 years of age survivors, but survivors with siblings gave significantly lower scores in PedsQL™ psychosocial health than the survivors with no siblings. Survivors <18 years of age who had needed remedial education at school scored significantly lower HRQL than those who had not needed. Lähteenmäki et al. (2002) have reported that survivors required statistically significantly more extra tutoring at school in Finland compared with their healthy siblings and healthy controls. This may mean that poorer success at comprehensive school correlates with lower HRQL or one could also assume that low HRQL leads to poorer school performance. Our result that the survivors <18 years of age who had an additional non-cancer illness showed significantly lower HRQL scores is quite reasonable: patients with a history of cancer diagnosis combined with some other disease may value their HRQL lower than those with no diagnoses.

Self-reported happiness explained most of the variation in HRQL scores such that unhappiness indicated lower HRQL scores. Our demographic questionnaires contained question "Do you feel happy?" This question was chosen because happiness is sometimes used interchangeably with QL/HRQL, although these are broader than happiness (Bekhet et. al. 2008). Happiness may be a more direct predictor of QL and depression than the intensity of treatment for cancer and, therefore, interventions that cultivate happiness may be effective ways to improve survivors' HRQL and decrease depressive symptoms regardless of gender or the intensity of treatment protocol (Bitsko et. al. 2008). Happiness is vital and important in maintaining health (Cohen 2002) and we need more research about happiness and its effects on HRQL and fatigue. Secondly, it has been shown that depressed mood and fatigue are related to each other. Stepanski et al. (2009) found that depressed mood acted directly to increase fatigue. Additionally, it acted indirectly through increasing troubles in sleeping in adult cancer patients. Especially, our finding on self-rated happiness explaining most of the variation in HRQL scores, may be an indicator of low sensitivity of the generic HRQL instruments with regard to verifying the disease specific aspects of HRQL. Some of the mental aspects may be such that are actively denied and cannot be assessed properly otherwise than by in-depth interviews.

When HRQL was analysed by the disease-related factors, the factors that appeared to have effect on HRQL were age at the time of diagnosis, diagnosis of Wilms tumor, neuroblastoma, or osteosarcoma, and SCT treatment. Higher age at the time of diagnosis, as well as a diagnosis of Wilms tumor or neuroblastoma indicated statistically significantly lower scores on HRQL for survivors below the age of 18 years. This is most probably because these survivors may have growth and other endocrinological problems due to intensive treatments with autologous SCT in our neuroblastoma group and radiotherapy or intensive therapy in our Wilms tumor group. The ≥18 years of age survivors of

osteosarcoma demonstrated more problems in mobility and hearing compared to the leukemia survivors and scored significantly lower on the physical functioning score. The latter result was in line with previous studies (Maunsell et al. 2006, Reulen et al. 2007). However, there are studies where diagnosis did not associate with HRQL scores (Apajasalo et al. 1996, Pemberger et al. 2005). In the analysis of HRQL by treatment group, survivors ≥18 years of age treated with SCT scored significantly lower HRQL scores than survivors who have been treated with surgery only. In the study of Sanders et al. (2010), adult childhood cancer survivors treated with SCT in childhood scored significantly lower in SF-36 PCS than the control group members but MCS scores were not significantly lower than those in the control group. Thus, our results seem to be valid even though the SCT group was small.

The factors which associated increasingly with survivors' fatigue were gender, age, the need of remedial education at school, over 10 years length of survival, and a sarcoma diagnosis. Our findings about male survivors having more problems with SF than females differ from the earlier studies (Langeveld et al. 2003, Perdikaris et al. 2008). Interestingly, in our study, gender did not have any significant effect on the fatigue scores of the control groups. Increased age was associated with more fatigue, especially with sleep related fatigue. Survivors who had needed remedial education at school scored more problems with SF. This may mean that poorer success at comprehensive school correlates with more fatigue. On the other hand, excess fatigue could lead to poorer school performance (Dewald et al. 2010). Our result that sarcoma diagnosis was associated with increasing fatigue is consistent with the previous results that young survivors of osteosarcoma and Ewing's sarcoma were more fatigued than the normative sample control group members (Aksnes et al. 2007). It could be possible that sarcoma patients' physical limitations and impairments after cancer treatment also affect their fatigue level later in life. Similarly to another adult cancer survivors' study (Servaes et al. 2002), such disease-related factors like treatment modality, relapse status or age at diagnosis did not have significant effect on any fatigue scores in our study. However, over 10 years length of survival time indicated statistically significantly more problems with SF than ≤10 year's length of survival. Our result that better HRQL score indicated statistically significantly fewer problems with all fatigue scores in our multivariate analysis was consistent with other studies as well (Eddy & Cruz 2007, Meeske et al. 2004, Meeske et al. 2007, Varni et al. 2002a).

The self-reported items that are causing worries or are rated as best things in survivors' lives

Our last aim was to describe the self-reported items that are causing worries or are rated as best things in the lives of young adults who have survived childhood cancer at least four years beyond cancer diagnosis. According to results of our open questions, the survivors are most worried about their physical health. The survivors were worried also about their mental health, cancer inheritance, late-effects, fertility and relapse issues. The health care professionals should pay more attention for discussing about these issues with the survivors in the future. Langeveld et al. (2004) found that many survivors have concerns

about the health of their future children as well. It is important that survivors do know the facts about these issues and do not worry unnecessarily. For example, they should know that the survivors' offspring are not in an increased risk of neonatal death, stillbirth or early mortality when comparing with their siblings. Neither have the offspring of survivors a risk of sporadic cancer. However, the offspring of female cancer survivors could have an increased risk of preterm birth and need of monitoring or intensive care in the neonatal period. (Madanat-Harjuoja et al. 2010a, Madanat-Harjuoja et al. 2010b) It seems that most survivors keep their family, friends and social relationships their best things in their life. The second most cited thing was their physical health. In general, the survivors and controls answers about their worries and best things were surprisingly similar and the same main issues rose in both groups.

6.2 Validity and reliability of the study

Certain limitations should be considered when interpreting the findings of our study. A total of 55.6% survivors of childhood cancer and 55.1% parents of survivors below 18 years of age participated in the study. A total of 595 controls and 253 controls' parent participated. The response rates seem acceptable for a postal survey (Asch et al. 1997). However, the controls' response rate could have been better if we had sent the questionnaire package for all controls at the same time and sent the reminder for those who did not respond, instead of aiming to get one control per one survivor. Attention must also be paid to the fact that many respondents were children, which could affect the response rate. Positive merit is that there were no significant differences between the demographic variables and clinical characteristics of respondent and non-respondent survivors according to the information received from the FCR, except that the ≥ 18 years old non-respondent survivors were more likely to be males.

The study strength is that controls were matched for age, gender and living place, which rules out a bias caused by possible differences between urban and rural populations. The other strength of our study was that we were able to use child-parent pairs for statistical analyses. There were no significant differences in the demographic variables between the survivors and their controls, other than the controls had more often siblings than the survivors in both age groups, and the ≥18 years of controls had needed less remedial education at comprehensive school than survivors. However, one may question whether some other group than healthy children could be a better comparison group when assessing the HRQL of a population that has experienced a severe illness. According to Eiser & Eiser (2000) the HRQL measured by self-report might be associated with different patterns of social comparisons. The persons could do an upward comparison, also called unfavorable comparison, where they compare themselves with those who are doing slightly better than themselves or do assimilation to a less desirable standard. On the other hand, a person could do the downward comparison, also called favorable comparison, where they compare themselves with those who are doing slightly worse than themselves, or a person might think that "*I'm doing just as well as most of my*

friends". This kind of comparisons could also influence with parent-proxy measurements. Eiser & Eiser (2000) found out that the mothers and survivors made more favorable than unfavorable comparisons to providing confirmation of the completeness of cure. Also the instruments SF-36 and PedsQL used in our study included some questions where one had to evaluate her/his HRQL in relation to others.

We cannot totally exclude the possible effect of responder-related selection bias on HRQL or fatigue. It may be possible that survivors with poorest HRQL or those most fatigued did not have energy to fill in the questionnaires. To avoid this possibility, we used parallel parent proxy-reports for survivors below 18 years of age (De Clerq et al. 2004, Eiser & Morse 2001, Schultz et al. 2007). On the other hand, those survivors who have no problems might not respond to questionnaires. However, one could assume that parents whose children have a poor HRQL or are fatigued would be most willing to reply.

Due to relatively small population in Finland, our study group was small. The registration of cancer cases to the Finnish cancer register started in 1953 and the data are complete for childhood cancers (Teppo et al. 1994). That is why we have, however, a unique data when comparing with any other international childhood cancer survival study. The study limitations are the lack of detailed treatment data and risk classifications in the FCR. Our study group can be also skewed in regard to the diagnosis. Other cancer survivor groups than leukemia group were small, because leukemia comprises of almost half of the extracranial childhood malignancies and the prognosis of leukemia is very good in Finland. When interpreting our results, one has to consider that our study is not strictly comparable with the very big studies like for example the American reports of childhood cancer survivors study group (Reulen et al. 2007), due to our different public health care and school system. Also nationwide health insurance coverage in the Scandinavian countries may have some impact on the general HRQL. Lack of health insurance could negatively affect survivors both when they were children or later in their life. Hence, long-term effects might differ in countries where access to health care is universal. (Maunsell et al. 2006)

Validity and reliability of the used instruments

The used HRQL instruments have been translated and validated in Finland earlier and two of them (PedsQL™ and SF-36) are the most used generic HRQL instrument internationally. Three of the instruments (15D, 16D and 17D) are developed in Finland and are also internationally used instruments. Only instrument that was not used, translated and validated before this study was the PedsQL™ Multidimensional Fatigue Scale. All the used instruments displayed acceptable reliability coefficient, and for total PedsQL™ it was as high as 0.91 for survivors and 0.90 for controls which are acceptable for group comparisons (Varni et al. 1999, Varni et al. 2001). Although generalized instruments are useful for longitudinal studies and when comparing HRQL or fatigue between the survivors and healthy controls, used instruments in this study might not

adequately reflect the experiences of cancer survivors (Pearce et al. 2008). Firstly, using the generic instruments based on a definition and theory of HRQL or fatigue designed for a healthy population, we may ignore the effects of the childhood cancer and the physical and emotional burdens placed on cancer survivors (Parsons & Brown 1998). Survivor's expressed their worries about their physical and mental health also in our open question. Secondly, disease experience also affects what is important for children, for example physical functioning for children with rheumatic disease could be more important than for example for children with diabetes (Varni et al. 2002b). In the future, we need more qualitative studies about what are important HRQL issues for childhood cancer survivors. Our open question showed that survivors were more concerned about their physical health than their controls. It seems that survivors have different perspective on their physical and mental health than their controls have. Thirdly, normalcy is highly valued by cancer survivors (Prouty et al. 2006) and living as normal life as possible is a way to manage the situation (Enskär & Berterö 2010). Thus, cancer survivors may have developed coping strategies, such as the need to be normal, to make the best of things (Rechner 1990, O'Leary et al. 2007) and therefore survivors may have a more positive view of life and themselves after cancer experience (O'Leary et al. 2007, Sundberg et al. 2009) than their healthy controls. Such as one survivor wrote in our open question about the best things in her life: *"Also it's being healthy and finally able to enjoy life and live to the fullest. I'm also happy that my health is good and I recovered from my illness. I feel healthier than ever before. I can do and enjoy things without my previous illness limiting me. Exercise is an important driving force that I wouldn't want to lose. Recovering from cancer gives me self-confidence and a belief in being able to cope with future challenges; it has helped me cope with many difficult issues. On the other hand even small things make me happy."* The significance and value of experiences of fatigue might be also markedly different for survivors than for healthy controls (Parsons & Brown, 1998).

Our results suggested that the PedsQL™ Multidimensional Fatigue Scale is a valid and reliable instrument for self-assessment and parent-proxy assessment of fatigue in children and adolescents. According to the cognitive interview, Finnish PedsQL™ Multidimensional Fatigue Scale was very easy to understand and easy to fill in. All participants gave very positive opinions on the questionnaire. The instructions and response choices were easy to understand, and participants had no trouble to find out a response choice that described their situation. However, interviewer noticed that no one did read instructions before they started to fill in questionnaires, but they were in anyway able to complete the questionnaire. Some interviewed participants told that it was a bit difficult to separate difference between seldom and sometimes. The questionnaire was not too long and each participant completed the questionnaire in less than 5 minutes. However, there were a few problems. Firstly, no one of the 8-12 year old children could tell what "in the past one-month" means and this reference period was not what participants used to determine their response, except one 13 year old girl. All the others said that they thought more commonly. Thus, when interpreting our results, we have to consider a possibility that younger children's reference period could vary from this

moment to feelings more commonly, not only for their fatigue in past one-month. The same could be true also in the used generic PedsQL™ 4.0 instrument. Secondly, one parent and one child wondered why this questionnaire did not ask any questions about school issues or hobbies. They thought that it is important to know also whether they are tired during the school day, and sometimes hobbies can also cause fatigue.

The percentages of missing values of Finnish PedsQL™ Multidimensional Fatigue Scale were 0.26% for the survivors self-report and 0.31% for their healthy controls self-report. For the survivors' parent proxy-report and healthy controls' parent proxy-report, the percentages of missing item responses were 0.43% and 0.27%, respectively. Internal consistency estimates of reliability using Cronbach´s alpha were computed on the total score and all three six-item subscales: general fatigue, sleep/rest fatigue, and cognitive fatigue scores for both child and parent proxy versions. The children's total fatigue score reliability coefficients ranged from 0.90 to 0.92 for survivors and 0.84 to 0.89 for their controls in PedsQL™ Multidimensional Fatigue Scales. The parent proxy total fatigue score reliability coefficients were 0.93 for the parents of survivors and 0.90 for the parents of healthy controls. All total scores in parent proxy report scales approached at least 0.70 reliability standards. However, the sleep/rest fatigue scores had the lowest internal consistency in all groups, for children 0.54-0.74 and for parent-proxy 0.71-0.82. The smallest internal consistency 0.54 was for controls from 13 to 18 years in sleep/rest fatigue score. Maybe this part of the questionnaire needs further clarification in the future, because also according to the interview, the question "*I sleep a lot*" was the most problematic question for some participants. The participants did not know whether the question asked that they sleep too much like an ill person or that they sleep like a person of their age should.

PedsQL™ Multidimensional Fatigue Scales gives an opportunity to evaluate different dimensions of fatigue, bringing up opportunity to view fatigue more deeply than a measure of severity alone. However, there are some problems of few available fatigue instruments for children and adolescent. Firstly, instruments (including PedsQL™ Multidimensional Fatigue Scales) do not separate acute and chronic fatigue, which could be an important aspect for childhood cancer survivors. It is possible, that childhood cancer survivors' fatigue is chronic. At least survivors who have been diagnosed before adolescence have identified fatigue as one part of their entire life and feel that fatigue still impacts negatively their daily lives (Langeveld et al. 2000). The second problem is the unknown cut-off score that is clinically relevant and meaningful for children's everyday life. However, the problems of fatigue instruments for adults are similar. Only a few instruments actually have suggested a cut-off score for a clinically relevant level of fatigue (Whitehead 2009). The solution to use cut-off scores taken from the control population's results is not an ideal as normal population can also be fatigued (Mears et al. 2004, ter Wolbeek et al. 2006).

6.3 Suggestions for future research and clinical practice

It has become obvious that in medical approach the quantity of survival is no longer perceived to be the only end-point. Evaluations addressing whether the treatment really makes patients feel better are deemed to be at least equally important. How to measure this "feel better" factor is a challenge, especially with children (Eiser & Morse 2001a) as well as with the population of childhood cancer survivors. More critical evaluation is needed in the future to compare different generic instruments and their feasibility in the population of childhood cancer survivors to find out whether the generic HRQL instruments are sufficiently sensitive enough and capable of capturing a sufficiently broad perspective of HRQL (Davis et al. 2006). Firstly, with generic instruments we cannot evaluate how the illness experience will affect person's life and maybe those instruments have not the right questions for childhood cancer survivors. Self-reported happiness for example, explained most of the variation in HRQL scores than any illness related factors. Secondly, because there is no systematic psychosocial care during the childhood cancer treatment available in hospitals, we could assume that the child's unhandled trauma experiences will later sprout in the life, affecting also their HRQL. Therefore, in the future, researchers need instruments that are specifically designed for assessing HRQL in young childhood cancer survivors (Woodgate 2008). Hence, in addition to using quantitative research methods, we also have to use more qualitative research methods to find out the unique perspective of HRQL in childhood cancer survivors (Cantrell 2007). In the future, researchers should resolve the question whether the generic standardized instruments are the best solution for the assessment of HRQL in childhood cancer survivors or, should we create more cancer-specific instruments and compare diagnostic subpopulations to each other instead of using the healthy population as a control?

In the future we also need fatigue instruments that are specially designed to childhood cancer survivors. Such that take into account their unique past fatigue experiences due to cancer treatment. Interventions to prevent fatigue in childhood cancer survivors should also be developed in the future. Unfortunately, we did not measure fatigue separately from over 18 years of age survivors. It is recommended that in the future also their fatigue level will be evaluated.

Being a cancer survivor will continue to affect some or all survivors' healthcare status later in their life. The most of the individuals surviving childhood cancer will live several decades with little or no contacts with healthcare professionals. (Parsons & Brown 1998) Survivors should be active participants in their own survivorship care, because they and their parents are the experts about their own health on a day-to-day basis (Shepherd & Woodgate 2010). It has been noticed that the percentage of survivors involved in follow-up programs decreases with the age of the survivor (Blaauwbroek et al. 2006). Health care professionals and pediatric care centres must communicate with each other to obtain accurate information about treatment exposures and their potential long-term adverse effects (Hudson et al. 2003). In Finland, we do not yet have centralized care for

adult childhood cancer survivors, which could help survivors to deal with their special cancer related needs later in their life. Hence, the systematic follow-up of all childhood cancer patients should be organized in Finland.

Health care professionals must also be aware of that the long-term survivors may have other expectations and goals with respect to their current health status (Sundberg et al. 2010). Those expectations and goals are recommended to be investigated with in-depth interviews, because the information one gets with questionnaires about survivors' HRQL may not be enough. Survivors' experiences can be so unique, that their feelings are hard to be put in a scale or they may not exist in the instruments (Woodgate 2008). Thus, in the future, we need still more information about how young cancer survivors value their HRQL as healthcare professionals (Jance et al. 2005) and researchers may have misunderstood the subjective HRQL attributes of this special group of patients.

6.4 Conclusions

Our study aimed to increase knowledge and understanding about the relationship between childhood cancer and its treatment and HRQL of childhood cancer survivors. In conclusion, it seemed that when using generic HRQL instruments, the majority of the young survivors of childhood cancer had a positive attitude and good HRQL after their cancer experience. Childhood cancer survivors over 18 years of age reported even higher HRQL than controls. However, there were subgroups of childhood cancer survivors who had poorer level of HRQL than the others.

The demographic factors that associated with poorer HRQL were female gender, greater weight, living alone, need of remedial education, an additional non-cancer diagnosis, survivors' with siblings, and self-rated unhappiness. When investigating disease-related factors, our results showed that especially the survivors of osteosarcoma and Wilms tumor or neuroblastoma had special needs that could influence their ability to live a normal life after childhood cancer. Also those survivors who had been treated with SCT were at risk for inferior HRQL as well as those survivors with higher age at diagnosis. Noteworthy is that all the used demographic and disease related factors explained only about one third of the variation in the HRQL scores. Thus, we still do not know which the key components of HRQL are for the survivors of childhood cancer. However, our results suggested that above mentioned survivors could benefit from ongoing long-term follow-up as there were many questions raised up regarding the cancer experience and the late-effects of cancer.

Even though survivors seem not to experience more fatigue than their matched controls, there were sarcoma patients who experienced excessive fatigue that may have impact on their HRQL. Male gender, older age, the need of remedial education at comprehensive school, lower overall average grade in the latest school marks report, length of survival more than 10 years, lower HRQL-scores, and a sarcoma diagnosis associated with

increasing fatigue level. The health care team should recognize the needs of those young survivors, particularly those with sleep fatigue, as soon as possible after cancer treatment in order to prevent their fatigue becoming chronic and to secure that they have energy for developmental tasks of childhood.

According to our results, the survivors of childhood cancer were worried about their physical and mental health. They had cancer related worries about cancer inheritance, late-effects, fertility and relapse issues. The survivors need more information about these areas. One could assume that more and better informed survivors will be satisfied, happier and more able to help themselves. Happiness, above all, seemed to influence the level of HRQL in childhood cancer survivors.

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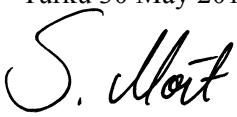

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